ECMTB'24

13TH EUROPEAN CONFERENCE ON MATHEMATICAL AND THEORETICAL BIOLOGY | JULY 22 - 26 | TOLEDO · SPAIN

BOOK OF ABSTRACTS

ESMTB
European Society for Mathematical and Theoretical Biology

UCLM

MATHEMATICAL ONCOLOGY LABORATORY

BENOIT PERTHAME & VÍCTOR MANUEL PÉREZ GARCÍA

Welcome letter

With great pleasure, we extend our warmest greetings to each of you as we come together to celebrate the 13th European Conference on Mathematical and Theoretical Biology!

Organized under the banner of the European Society for Mathematical and Theoretical Biology (ESMTB), this conference represents a new step in the series of events that have been advancing the intersection of biology and mathematics. The ESMTB, as a learned society, has been at the forefront of nurturing and promoting theoretical approaches and mathematical tools in the realms of biology and medicine across Europe and beyond.

We are delighted to welcome all of you, esteemed researchers, scholars, and enthusiasts, to join us in this intellectual endeavor. The ECMTB conferences represent the pinnacle of our community's collective efforts, providing a platform for sharing research, fostering collaboration, and igniting new ideas. Your presence here not only enriches this event, but also contributes to the larger purpose of driving scientific progress and innovation.

As we embark on this journey together, we encourage you to actively participate by sending proposals for minisymposia, contributed talks, or posters. Your contributions will play a vital role in shaping the diversity and richness of the conference program, furthering our collective knowledge and exploration at the interface of mathematics and biology.

Once again, a warm welcome to all of you! Let us make the 13th European Conference on Mathematical and Theoretical Biology an unforgettable gathering that inspires us to reach new heights in our understanding of this fascinating discipline.

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PLENARY TALKS

Christina Cobbold

UNIVERSITY OF GLASGOW

The role of individuals and their traits in determining the impacts of environmental change: from blowflies to mosquitoes

Environmental change is having profound effects on populations from dramatic global declines in biodiversity to increased incidence and geographical spread of vector borne diseases, such as dengue. Predicting complex species-environment interactions is crucial for guiding conservation and mitigation strategies in a dynamically changing world. Many individual organisms can rapidly respond to their changing environment through phenotypic plasticity, where variable traits are expressed depending on environmental conditions experienced. For individuals, the effects of phenotypic plasticity can be quantified by measuring environment–trait relationships, but it is often difficult to predict how phenotypic plasticity affects dynamics at the level of the population. I will present a mathematical framework for capturing the interaction of environment, individuals and their traits to establish the role of phenotypic plasticity in mitigating the effects of climate change. I will show how this approach leads to both interesting mathematical questions and novel dynamics and can be used to helping to explain the location, magnitude and timing of historical dengue outbreaks.

Evrim Acar Ataman

SIMULA

Extracting Insights from Complex Data using (Coupled) Tensor Factorizations

There is an emerging need to jointly analyze data sets collected from multiple sources in order to extract insights about complex systems such as the human brain, or human metabolome. For instance, joint analysis of omics data (e.g., metabolomics, microbiome, genomics) holds the promise to improve our understanding of the human metabolism and facilitate precision health. Such data sets are heterogeneous – they are a collection of static and dynamic data sets. Dynamic data can often be arranged as a higher-order tensor (e.g., subjects by metabolites by time) while static data can be represented as a matrix (e.g., subjects by genes). Tensor factorizations have been successfully used to reveal the underlying patterns in higher-order tensors, and extended to joint analysis of multimodal data through coupled matrix and tensor factorizations (CMTF). However, jointly analyzing heterogeneous data sets still has many challenges, especially when the goal is to capture the underlying (time-evolving) patterns. In this talk, we discuss CMTF models for temporal and multimodal data mining. We focus on a flexible, accurate and computationally efficient modelling and algorithmic framework that facilitates the use of a variety of constraints, loss functions and couplings with linear transformations when fitting CMTF models. Through various applications, we discuss the advantages and limitations of available CMTF methods.

Patricia Reynaud-Bouret

UNIVERSITÉ CÒTE D'AZUR

Hawkes processes and other variants to understand functional connectivity in the Brain

Hawkes processes are point processes that can model the emission of action potentials by neurons inside a network. We can use it to find the patterns of dependence that the neurons might exhibit as a function of a state, a behavior or a stimulus. Therefore we have access to a functional view of the connectivity in the brain. This view is more complex than the firing rate coding notion, which is a notion at the level of a given neuron. Here we have access to the coding ability of the network as a whole, even if it is partially observed. After describing the potential of the Hawkes process in terms of interpretation and decoding, I will also explain how to expand this model to include the other electrical activity that can be recorded in the brain: the local field potential.

Ivana Bozic

UNIVERSITY OF WASHINGTON

Quantifying the evolutionary dynamics of cancer

Cancer results from a stochastic evolutionary process characterized by the accumulation of mutations that are responsible for tumor initiation, progression, immune escape, and drug resistance, as well as mutations with no effect on the phenotype. Mathematical modeling, combined with clinical, sequencing and epidemiological data, can be used to describe the dynamics of tumor cell populations and to obtain insights into the hidden evolutionary processes leading to cancer. I will present recent approaches for quantifying the evolutionary dynamics of cancer in patients, and their implications for deciphering cancer heterogeneity and response to therapy.

Ganna Rozhnova

UNIVERSITY MEDICAL CENTER UTRECHT

Controlling COVID-19 with Vaccination: Lessons Learned and Open Questions

Vaccination is the main pharmaceutical intervention to reduce COVID-19 hospitalizations. I will present an assessment of the impact of SARS-CoV-2 vaccination strategies during the pandemic and in the post-pandemic period. The quick development and rollout of vaccines around the world opened possibilities for relaxing non-pharmaceutical interventions during the pandemic, but it was only with the large-scale rollout of vaccination that effective control of COVID-19 transmission was achieved. In the post-pandemic period, SARS-CoV-2 infection causes common cold- or flu-like illness in most individuals, but patients with chronic conditions still experience a higher chance of COVID-19 hospitalization. It is crucial to estimate COVID-19 burden in chronic patients and to determine how best to protect them from severe COVID-19. I will consider several age-structured models that have been fitted to age-specific data sources. The model population is stratified by age, risk due to chronic conditions, and immunity level. To stratify the population into risk groups due to pre-existing chronic conditions (low-, moderate-, and high-risk), I will compare the European classification by the European Centre for Disease Prevention and Control and the national classifications by the public health institutes in individual European countries. I will consider several strategies, namely vaccination of high-risk individuals, high- and moderate-risk individuals, individuals above 60 or 80 years old, and combinations of these strategies. I will discuss how best vaccination strategies differ depending on the metrics used for their evaluation: 1) maximum vaccination impact as quantified by the reduction in the number of hospitalizations due to vaccination; 2) maximum vaccination effectiveness as quantified by the number needed to vaccinate to prevent one hospitalization.

Mustafa Khammash

ETH ZURICH

Designing Robust Biomolecular Control Systems for Perfect Adaptation

Adaptation is a recurring theme in biology, offering vital survival mechanisms in dynamic environments through precise regulation of physiological variables. In this talk, I will present the fundamental theory and concepts needed for designing biomolecular control systems that achieve robust perfect adaptation (RPA). RPA is a biological process through which a specific variable of interest is maintained at a desired setpoint despite persistent perturbations in the underlying network. From a theory perspective, I will elucidate how RPA imposes critical structural constraints on the underlying networks that can be characterized by simple linear algebraic conditions. These conditions in turn impose an integral feedback structure on RPA achieving networks, a fact that yields insight into how RPA mechanisms can be realized with biomolecular reactions. Building on these insights, I will introduce a novel internal model principle (IMP) tailored for biomolecular networks, akin to celebrated IMP in control theory. Finally, I will relate these theoretical developments to practical implementation of RPA-achieving controllers and their applications. I will demonstrate the implementation of genetically engineered synthetic RPA controllers in living cells and showcase their tunability and adaptation properties.

Anna Marciniak

HEIDELBERG UNIVERSITY

Evolution of heterogeneous cellular systems: Mechanistic mathematical modelling to uncover the dynamics of developmental cell hierarchies in regeneration and cancer

Stem cells in adult tissues generate cells needed for plasticity, growth and repair, and play a critical role in the development of cancer. Proper system performance requires a continuous capacity of stem cells to self-renew and differentiate, called stemness, which must be robustly regulated at the cell population level. The system typically exhibits great heterogeneity at the single cell level, which evolves in time and space. It is not yet understood if and how this heterogeneity contributes to the control of the system. In this talk I will discuss mathematical approaches to modelling and analysing stem cell transitions. Inferring information about the control of stem cell dynamics from single cell data requires combining statistical data analysis with mechanistic models of stem cell self-renewal and differentiation. A new class of structured population models can describe the evolution of cell distributions in the feature space revealed by single cell omics, which can be defined in terms of the measure differential equations. Theoretical concepts and modelling challenges will be discussed using examples of adult neurogenesis and glioblastoma, in particular the role of cellular hierarchies in cancer progression and model-based data analysis.

PRIZE TALKS

James Holehouse

University of Edinburgh, UK

Breaking steady state assumptions in models of stochastic chemical kinetics

Randomness in chemical kinetics and gene expression lies at the heart of our understanding of biological function. Stochasticity in the intrinsic components of gene expression leads to non-genetic heterogeneity that is thought to be important in the evolution of cancer cells, but also in the ability of healthy cells to survive conditions of environmental stress. It can lead to behaviours that are phenomenologically distinct from deterministic models of the same systems; in some cases deterministic models can make exactly the wrong predictions. In this talk, I will focus on a part of my PhD thesis dedicated to the breaking of Markovian steady state assumptions in stochastic kinetics. In particular, I will explore how we can mathematically look beyond the “biological steady state” regime, introduce path-dependence in otherwise memoryless models, and the interesting behaviours and kinetics that are encoded in the dynamics through which systems relax to their steady states. Finally, I will reflect on what makes a successful PhD experience, the importance of good mentorship, and the importance of “spin-off” projects, and why academic spin-offs are typically more successful than those of sit-coms.

2023 Reinhart-Heinrich Doctoral Thesis Award

Kishori Hari

Indian Institute of Sciences

Design Principles of Phenotypic Robustness and Plasticity in Gene Regulatory Networks underlying Cancer Metastasis

CONTRIBUTED TALKS

COUPLING CELL SIZE REGULATION AND PROLIFERATION DYNAMICS OF MICROBES REVEALS CELL DIVISION BASED ON SURFACE AREA

Abhyudai Singh (University of Delaware)
Other authors: César Nieto, Sarah Täuber, Luisa Blöbaum, Zahra Vahdat, Alexander Grünberger.

Single cells actively coordinate growth and division to regulate their size, yet how this size homeostasis at the single-cell level propagates over multiple generations to impact clonal expansion remains fundamentally unexplored. Classical timer models for cell proliferation (where the duration of the cell cycle is an independent variable) predict that the stochastic variation in colony size will increase monotonically over time. In stark contrast, implementing size control according to adder strategy (where on average a fixed size added from cell birth to division) leads to colony size variations that eventually decay to zero. While these results assume a fixed size of the colony-initiating progenitor cell, further analysis reveals that the magnitude of the intercolony variation in population number is sensitive to heterogeneity in the initial cell size. We validate these predictions by tracking the growth of isogenic microcolonies of Corynebacterium glutamicum in microfluidic chambers. Approximating their cell shape to a capsule, we observe that the degree of random variability in cell size is different depending on whether the cell size is quantified as per length, surface area, or volume, but size control remains an adder regardless of these size metrics. A comparison of the observed variability in the colony population with the predictions suggests that proliferation matches better with a cell division based on the cell surface. In summary, our integrated mathematical-experimental approach bridges the paradigms of single-cell size regulation and clonal expansion at the population levels. This innovative approach provides elucidation of the mechanisms of size homeostasis from the stochastic dynamics of colony size for rod-shaped microbes.

A HOUSEHOLD MODEL FOR THE INTRODUCTION OF WOLBACHIA TO CONTROL DENGUE

Abigail Barlow (The University of Bath)
Other authors: B. Adams

Dengue is a common vector-borne disease. It is transmitted between humans by Aedes mosquitoes. It is widespread throughout tropical and subtropical regions, particularly urban areas. Wolbachia is an intracellular bacteria that can infect Aedes mosquitoes. Infection inhibits vector competence and so the release of Wolbachia-positive mosquitoes can help control dengue.

In this talk we introduce a mathematical model for the release of Wolbachia-infected mosquitoes at the household scale. We use a continuous time Markov chain framework to investigate the dynamics of the introduction, quasi-stationary distributions and the probability of households reaching a state in which all resident mosquitoes are Wolbachia-infected. We extend the model in an a ordinary differential equation framework to examine the impact of the movement of mosquitoes between households.

ASSESSING NEURAL NETWORK MODELS OF MOSQUITO ABUNDANCE FOR VECTOR SURVEILLANCE

Adrienne Kinney (University of Arizona)
Other authors: J. Lega

Vector-borne disease outbreaks are closely tied to vector abundance, which makes knowledge of population dynamics useful in preventing future outbreaks. Here we use the Aedes-AI framework we previously developed to produce probabilistic forecasts of mosquito abundance for neighborhoods in Puerto Rico.

The Aedes-AI models are a collection of neural network models of Aedes aegypti abundance [1]. The models are trained on synthetic data generated from a mechanistic model, in contrast to other models of mosquito abundance that rely on noisy, real world trap data for training. We previously demonstrated that the neural networks can learn the spatiotemporal features of mosquito populations.

In this work, we use the Aedes-AI models to generate predictions using local weather and present a methodology of scaling the predictions and forecasting mosquito abundance based on past trap data. We assess the ability of the forecasts to capture trends in future trap data and compare them with outbreaks of mosquito-borne diseases in the region. We conclude with a discussion on how the Aedes-AI models are appealing from a public health perspective and can be used to supplement vector surveillance efforts.

[1] Kinney, A. C., Current, S., Lega, J. (2021). Aedes-AI: Neural network models of mosquito abundance. PLOS Computational Biology, 17(11), e1009467.
https://doi.org/10.1371/journal.pcbi.1009467

A MATHEMATICAL STUDY ON STONE SUBAERIAL BIOFILMS

Alberto Tenore (University of Naples Federico II)
Other authors: F. Russo, J. Jacob, J.D. Grattepanche, B. Buttaro, I. Klapper

Subaerial biofilms, intricate microbial communities thriving on terrestrial surfaces, play a crucial role across various scientific fields, influencing cultural heritage preservation, microbial ecology, biogeochemical cycling, and biotechnology. Inspired by experimental observations on the marble surfaces of famous monuments, this study presents a mathematical model capturing the intricate dynamics of stone subaerial biofilms (SABs), with a main focus on the ecology and metabolic interplay between cyanobacteria and heterotrophs. SABs are modeled as thin mixed biofilm-liquid water layers sitting on stone. A system of ordinary differential equations regulates the dynamics of key SAB components: cyanobacteria, heterotrophs, polysaccharides and decayed biomass, as well as cellular levels of organic carbon, nitrogen and energy. These components are interconnected through a network of metabolic pathways, modeled with limitation terms reflecting the impact of biotic and abiotic factors. Temperature, humidity, and light intensity are considered as input model variables that regulate microbial activity by influencing water availability and metabolic kinetics. Relevant physico-chemical processes, including pH regulation, further contribute to a comprehensive description of the SAB ecology. Numerical simulations explore the dynamics of SABs in a real-world context, revealing distinct daily activity periods shaped by water activity and light availability. These factors impact metabolic rates and microbial composition, showcasing the adaptive capacity and resilience of SAB ecosystems across diverse environmental conditions. Additionally, the numerical investigation emphasizes the key contribution of cyanobacteria as a fundamental resource for heterotrophs. The results also suggest that heterotrophs, on the other hand, could play a substantial role in decomposing waste organic carbon and regulating pH, thus influencing the overall composition and stability of the biofilm.

ACCIDENTAL AND REGULATED CELL DEATH IN YEAST BIOFILMS

Alex Tam (The University of South Australia)
Other authors: D. Netherwood, E. Green, C. Gourlay, V. Jiranek, B. Binder

The yeast species Saccharomyces cerevisiae (the budding yeast) is one of the most widely studied model organisms in molecular and cell biology. Budding yeast can form biofilms, in which cells reside in a self-produced extracellular matrix. Biofilm formation makes yeasts highly resistant to antimicrobial therapy and is a key reason for the major health burden of yeast infections. Lab-grown biofilms provide a way to study the mechanisms of growth relevant to pathogenic yeast species.

A central feature of yeast biofilms is cellular demise, which occurs by one of two independent mechanisms: accidental cell death (ACD) or regulated cell death (RCD). In this talk, we describe a reaction—diffusion equation (RDE) model for the nutrient-limited growth of a yeast biofilm, including the effects of ACD and RCD. The model consists of a coupled system of four non-linear RDEs for the yeast cell density, nutrient concentration, and two species of dead cells. Numerical solutions of the governing equations reveal that cell death due to RCD occurs in a localised annular region, which propagates with the biofilm as it expands. In contrast, ACD occurs in a circular region, which trails the expanding annular region of RCD cells. These numerical predictions provide good qualitative agreement with experiments.

This work is supported by the Australian Research Council Discovery Program (Grant numbers DP230100406 and DE240100897).

THE WELLS-RILEY MODEL REVISITED: RANDOMNESS, HETEROGENEITY AND TRANSIENT BEHAVIOURS

Alexander J. Edwards (EPSRC Centre for Doctoral Training in Fluid Dynamics, University of Leeds)
Other authors: MF. King, C. J. Noakes, D. Peckham, M. López-García

Providing a risk assessment for the transmission of airborne infections is a useful tool, and can give an insight into the factors that govern an outbreak. However, it is important that these quantitative methods consider scenarios which are as representative of reality as possible. Methodology such as the tradition Wells-Riley model are able to provide quick and easy risk assessments but fail to capture realistic features such as transient behaviour, or stochasticity and unknown parameters. In this work, we present mathematical models that build on the methodology of the Wells-Riley framework by including stochastcity, deriving a probability distribution for both the steady-state and transient quanta concentration solution. Through various extensions of this, we then explore explicit solutions for the probability of infection for scenarios such as after the infector leaves, an unknown duration, and unknown infectiousness. We illustrate the use of these methodologies through two case studies: an infectious health-care worker (HCW) who enters and leaves a space where the susceptible individual remains, and an outbreak during meal times in different dining settings for a random duration. The results highlight that infection risk to a susceptible who remains in the space after the infector leaves is non-negligible, and further illustrate the importance of exposure length and particular ventilation rates in influencing the outcome of an outbreak. Our methodological advances demonstrate the importance of using quantitative techniques that encapsulate the randomness and stochasticity that exists when replicating real-life scenarios to assess the risk of infection.

MODELLING TUMOUR ESCAPE MECHANISMS IN CAR T-CELL TREATMENT OF LEUKEMIAS.

Alexis Farman (University College London)
Other authors: Prof. Karen Page

A novel form of cancer immunotherapy, known as CAR T-cell therapy, has sparked significant enthusiasm amongst researchers and oncologists due to its effectiveness in treating various blood cancers. In leukaemia patients, the application of this therapy triggers a massive expansion of CAR T-cells, leading to a rapid reduction of the number of cancer cells to undetectable levels. Subsequently, the CAR T-cell population contracts, entering a sustained low-level state, primarily composed of Central Memory cells. Clinical observations have indicated that the loss of this persistence may result in patient relapse, prompting extensive research to uncover why immune persistence is so crucial. We employ a diverse array of analytical and numerical techniques to model the interactions between blast cells and immune cells. We use Ordinary Differential Equations (ODEs) to accurately depict the initial expansion and contraction phases of CAR-T cells and identify parameter regimes that yield a low tumour burden steady state. We use Stochastic Differential Equations (SDEs) and the Gillespie algorithm to study the stochastic effects at this steady state, with a focus on the role that immune persistence plays in deciding the outcome of the tumour (resurgence and escape or elimination). We will also develop models for escape mechanisms based on clinical observations and fit these models to clinical data. Our emphasis is on investigating specific immunosuppressive mechanisms, including the emergence of an immune-resistant phenotype, the existence of primitive blast stem cells able to escape recognition by CAR T-cells, and the presence of a spatial niche where blast cells can evade detection. Understanding these mechanisms is crucial as achieving prolonged persistence of CAR T-cells proves very challenging.

ATTRACTION AND REPULSION WITHIN CELL POPULATIONS ON GROWING SPATIAL DOMAINS

Alf Gerisch (TU Darmstadt, Department of Mathematics)

The collective migration of embryonic neural crest (NC) cells is of interest in its own right but also as a paradigm system for collective cell migration and pattern formation in general, see Reference [1]. NC cells migrate in streams away from the neural tube along well-defined paths to reach their destination. This results in an essentially one-dimensional spatial domain.

In this presentation we focus on two aspects which have been implicated in NC cell migration: spatial domain growth and contact-induced repulsion. The latter effect is modelled by a phenomenological non-local repulsion term, see Reference [2].

In the presentation we first discuss aspects of the continuous integro-differential model and then consider a range of approaches to address the numerical challenges due to the combination of a growing one-dimensional spatial domain and the efficient approximation of the non-local term. We present some simulation results and discuss their relation to experimental observations. Finally, we also include a short discussion of numerically solving similar non-local systems on two-dimensional spatial domains, which adds considerable complexity.

[1] Giniunaite, Rasa et al. (2019). Modelling collective cell migration: neural crest as a model paradigm. Journal of Mathematical Biology, 80(1-2), 481-504.
https://doi.org/10.1007/s00285-019-01436-2
[2] Painter, K. J. et al. (2015). A Nonlocal Model for Contact Attraction and Repulsion in Heterogeneous Cell Populations. Bulletin of Mathematical Biology, 77(6), 1132-1165.
https://doi.org/10.1007/s11538-015-0080-x

PANTOGRAPH TYPE PARTIAL DIFFERENTIAL EQUATIONS AND TUMOR GROWTH

Ali Ashher Zaidi (Department of Mathematics, Lahore University of Management Sciences, Lahore, Pakistan)

Other authors: B. van-Brunt, S. Taylor, B. Baguley, G.C. Wake.

Human tumour growth is constrained by a vascular cage. A recent study identifies two population cohorts in tumour tissue that play a key role [1]. We create a model that reflects recent medical progress, captures the concept of the two-cohort interaction, but is simple enough to study mathematically. The model involves at least two coupled nonlinear, nonlocal partial differential equations (PDE's). The mathematical tools to study properties of the solutions (particularly the long-time asymptotic behaviour) is central to the research. There is a paucity of mathematical information about such systems: this is a first foray into coupled systems of nonlocal PDE's of the coagulation-fragmentation type.

[1] Moser, Justin et al. (2018). Control of the Restriction Point by Rb and p21. Proceedings of the National Academy of Sciences, 115(35). https://doi.org/10.1073/pnas.1722446115

CRITICAL GAP SIZE

Ali Beykzadeh (University of New Brunswick)

This study explores the persistence of a population within a single patch with hard boundaries, such as a lake, implying that no disperser exits the habitat. A potential gap, like a fishing zone, divides the population within the patch. We present a method to calculate the maximum size of the gap that does not affect the stability of the population's non-zero steady state. The population's life cycle is modelled by a one-dimensional domain integrodifference equation (IDE). This approach separates the reproduction and dispersal phases in the species' life cycle. We develop an implicit function that is linked two key aspects: the demography and dispersal parameters of a species, and the total length of the non-reproductive gap. The function establishes a relationship between the dominant eigenvalue and the maximum length of the gap beyond which the population would collapse. We found that when individuals are more likely to settle in the fishing zone, or when they move slower in it and spend more time there, the fishing area must be shorter, and the no-take length must be larger to maintain the population in the lake. The relationship between the reproduction rate of the species in the no-take area and the optimal length of the fishing zone indicates that a longer fishing zone requires a higher reproduction rate in the no-take area to sustain the total population in the lake. This ensures that the no-take sides of the lake can support each other and prevent population collapse.

[1] Musgrave, J., Lutscher, F. (2013). Integrodifference equations in patchy landscapes. Journal of Mathematical Biology, 69(3), 583-615. https://doi.org/10.1007/s00285-013-0714-2

IDENTIFIABILITY AND OBSERVABILITY FOR A CLASS OF EPIDEMIOLOGICAL MODELS

Alicja B. Kubik (Universidad Complutense de Madrid and Instituto de Matemática Interdisciplinar)
Other authors: A. Rapaport, Á.M. Ramos, B. Ivorra

Mathematical modelling is widely used for the study of epidemics. Some of the most famous models are the so-called compartmental models, which separate the population in different disjoint groups attending to their health state: for example, the broadly known Susceptible, Infectious and Recovered compartments. These models are usually systems of ODEs, which are the ones we are going to address.

A typical methodology to apply these models to a real epidemic is the following: setting a model considering the main known features of the disease, looking for the parameters that are available in the literature, and recollecting real data series to calibrate the remaining parameters and (if necessary) initial conditions. However, before doing such a calibration, one can wonder the following: given the known data, can we recover the unknowns univocally? This question is addressed by the theories of identifiability and observability.

Both identifiability and observability theories have been widely used in different fields, such as bioreactors, navigation, or electronics. However, it is not that common in epidemics [1]. In this work, we present a class of systems such that, under some hypotheses, we can identify and observe them. Moreover, we provide a constructive way to recover both the initial conditions and the parameters. Many epidemiological models are included in this class of systems; in particular, we will illustrate this theory through some basic examples.

[1] Cunniffe, N., et al. (2023). Observability, Identifiability and Epidemiology - A survey. arXiv. https://doi.org/10.48550/arXiv.2011.12202

EXACT SOLUTIONS AND CONSERVATION LAWS OF A ONE-DIMENSIONAL PDE MODEL FOR A BLOOD VESSEL

Almudena P. Márquez (University of Cadiz)
Other authors: S.C. Anco, T.M. Garrido, M.L. Gandarias

Two aspects of a widely used 1D model of blood flow in a single blood vessel are studied by symmetry analysis, where the variables in the model are the blood pressure and the cross-section area of the blood vessel. As one main result, all travelling wave solutions are found by explicit quadrature of the model. The features, behaviour, and boundary conditions for these solutions are discussed. Solutions of interest include shock waves and sharp wave-front pulses for the pressure and the blood flow. Another main result is that three new conservation laws are derived for inviscid flows. Compared to the well-known conservation laws in 1D compressible fluid flow, they describe generalized momentum and generalized axial and volumetric energies. For viscous flows, these conservation laws get replaced by conservation balance equations which contain a dissipative term proportional to the friction coefficient in the model.

SPATIAL CHARACTERISATION OF RESIDUAL DISEASE IN ENVIRONMENTALLY MEDIATED DRUG RESISTANCE.

Amy Milne (Swansea University)
Other authors: A. Anderson, N. Picco.

Drug resistance is a major drawback of using molecularly targeted therapies to treat cancer. Early treatment success is followed by relapse [1]. This resistance has been shown to be driven by interactions in the tumour microenvironment, in particular the crosstalk between cancer and cancer associated fibroblasts (CAFs), resulting in residual disease [1]. Meads et al names this resistance environmentally mediated drug resistance (EMDR). Crucially EMDR is temporary where following a break in drug delivery, some additional therapeutic success can be achieved by the same drug. By introducing breaks in drug delivery, tumour growth can be modulated, and the time till progression extended, both of which are good outcomes for patients. Furthermore, limiting EMDR is beneficial to reducing the long-term development of more permanent resistance and complete treatment failure [1]. It is important to understand how the local interactions between cancer and CAFs lead to regions of residual disease. CAFs compete with cancer for space and resources while also contributing to the survival of cancer in stressful conditions. The interactions and crosstalk between cancer and CAFs depend on local conditions and result in complex residual disease dynamics at tissue level. We present a hybrid discrete-continuum model to capture the spatial information of a tumour undergoing molecularly targeted therapy. The model is calibrated using experimental data. Our model captures the emergence of EMDR while drug is delivered, where CAFs proximal to cancer in stress respond by producing growth factors sufficient for cancer survival. With our model we investigate intermittent treatment schedules that inhibit tumour growth. We also analyse the spatial information in regions of residual disease and regions where disease is eradicated. We characterise resistance patterns that emerge from the complex dynamics that occur in different temporal and spatial scales.

[1] Hirata, Eishu et al. (2015). Intravital Imaging Reveals How BRAF Inhibition Generates Drug-Tolerant Microenvironments with High Integrin β1/FAK Signaling. Cancer Cell, 27(4), 574-588. https://doi.org/10.1016/j.ccell.2015.03.008

MICROENVIRONMENT ANISOTROPY DRIVES CELL MIGRATION AND LARGE-SCALE NUCLEAR DEFORMATIONS - A COUPLED IN SILICO AND IN VITRO STUDY

Ana Bensabat Paulino (CFisUC, Departamento de Física)
Other authors: C. Leclech, M. Gouveia, J. Carvalho, R. Travasso, A. Barakat

Active cell migration is essential in diverse processes that sustain complex life forms, from morphogenesis to leukocyte chemotaxis in immune response. Cell migration is the result of intricate mechanisms that involve the coordination between mechanical forces, biochemical regulatory pathways, and environmental cues. In this work, we use a coupled in silico and in vitro approach to explore the pivotal role played by the anisotropy of the cell microenvironment in polarizing migrating cells and guiding cell movement. With this aim, we characterize the migration of endothelial cells and myoblasts in a substrate etched with narrow parallel microgrooves. We observe that the cells migrate in the groove direction and that the cell nucleus becomes caged, i.e. fully confined, within the microgrooves. This caging remains present, albeit to a smaller extent, when the cytoskeleton of the cell is disrupted, and its dynamics is associated with the nucleus membrane stiffness.

Moreover, we explore computationally the cell morphology by implementing a phase-field model of the interaction between the cell and the microgrooved substrate. This phase-field model includes the cell-substrate adhesion as well as the cell membrane and nucleus membrane bending rigidities. We observe that the fraction of nuclei caged in the microgroove is a function of two parameters: it decreases with the ratio between the cell membrane bending rigidity and the cell-substrate adhesion energy and it increases with the ratio between the cell membrane and nucleus membrane bending rigidities. We extend the model by including the dynamics of polymerization and depolymerization of actin inside the cell to model migration along the substrate microgrooves and to draw conclusions regarding the driving migrating mechanisms in these anisotropic microenvironments.

[1] Leclech, Claire et al. (2023). Distinct Contact Guidance Mechanisms in Single Endothelial Cells and in Monolayers. Advanced Materials Interfaces, 10(14).
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A MATHEMATICAL APPROACH TO THE EVOLUTION OF THE PROLIFERATION POTENTIAL OF STEM CELLS

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Stem cells are undifferentiated cells that can differentiate into the three germinal layers that give rise to all cells of the organism.Tracking human stem cells is complicated for numerous reasons. That is why we consider studying their evolution by means of mathematical models, which will help us to obtain clues to guide the work in the laboratory. We focus on models that classify the population according to telomeric length, or in other words, proliferation potential. The mean proliferation potential of the cell population was introduced as an indicator of ageing. The influence of telomerase activity on the evolution of the mean proliferation potential in healthy individuals with different telomere length percentiles was studied. Then, for patients with primary ovarian insufficiency, the impact of treatments with different telomerase levels was simulated. Sexual steroids ameliorated cell proliferation potential but not as in the healthy population. Gene therapy with adeno-associated virus made the proliferation potential similar to that of healthy people.

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GENOTYPE-STRUCTURED EPIDEMIOLOGICAL MODELS TO GAIN INSIGHTS INTO VARIANT EMERGENCE AND COMPETITION

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Phenotype-structured models were developed to gain crucial insights into evolutionary processes shaping cancer and viral infections. They offer a flexible way of integrating the evolutionary mechanisms into population dynamics models. In this work, we propose for the first time to integrate phenotype-structure into infectious disease models. We extend a previously developed SIR model with immunity by structuring infected individuals according to the phenotype of the virus that they are harbording and describe virus evolution as a diffusion process. After calibrating the model, we apply it to identify the factors that promote variant emergence. We demonstrate that factors such as a high basic reproduction rate, an increased mutation rate, broader cross-protection, and reduced genotypic differences between variants all contribute to the emergence of new variants. Then, we use the model to quantify the impact of variant emergence depending on the characteristics of the original and emerging variants, population-immunity, and the mutation rate. Our simulations reveal that broad cross-immunity is necessary for the eradication of the original variant following the emergence of a more transmissible one. Finally, we show that a robust and cross-variant immunity reduces the frequency of waves driven by virus evolution and immune waning. This approach can be adapted for different viruses and utilized to predict the emergence of specific variants based on genomic data, such as phylogenetic trees.

DYNAMICS OF POSITIONAL INFORMATION IN THE VERTEBRATE NEURAL TUBE

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In developing embryos, cells acquire distinct identities depending on their position in a tissue. Secreted signaling molecules, known as morphogens, act as long-range cues to provide the spatial information that controls these cell fate decisions. In several tissues, both the level and the duration of morphogen signaling appear to be important for determining cell fates. This is the case in the forming vertebrate nervous system where antiparallel morphogen gradients pattern the dorsal-ventral axis by partitioning the tissue into sharply delineated domains of molecularly distinct neural progenitors. How information in the gradients is decoded to generate precisely positioned boundaries of gene expression remains an open question. Here, we adopt tools from information theory to quantify the positional information that neural cells receive and investigate how temporal changes in signaling influence patterning precision. The results reveal that the use of signaling dynamics, as well as signaling level, substantially increases the precision possible for the estimation of position from morphogen gradients. This analysis links the dynamics of opposing morphogen gradients with precise pattern formation and provides an explanation for why cells rely on time-varying signals to impart positional information.

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BEYOND R0: EXPLORING NEW APPROACHES

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The basic reproduction number, denoted as R0, is a crucial parameter in infectious disease modeling and serves as a key element for designing control strategies. Calculating R0 can be challenging in certain situations due to the complexity of the model. This complexity often hinders the explicit computation of R0 and makes it difficult to understand how different populations and parameters influence its value. Recent research has introduced the concept of the target reproduction number as an alternative to R0. The target reproduction number demonstrates how it is possible to exert control over the entire system, by analyzing some subsystems that describe the behavior of an infectious disease, it is possible to exert control over the entire system. The target reproduction number offers a framework for making decisions in public health. In this study, we apply it to two models: a model involving incomplete vaccination and a model for leptospirosis. The presented models showcase two fundamental features of the target reproduction number. Firstly, its expression's simplicity compared to the basic reproduction number. Secondly, its behavior analogous to R0 at 1.

IDENTIFYING THE NUMBER OF RATE-LIMITING STEPS IN TRANSCRIPTION INITIATION, MRNA SPLICING AND NUCLEAR EXPORT FROM MRNA COUNT DATA

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What features of transcription can be learnt by fitting mathematical models of gene expression to mRNA count data? Selecting the optimal model can be achieved by fitting a suite of stochastic models to experimental data and comparing appropriate selection criteria. However, it remains unclear how useful this methodology is in identifying likely transcriptional mechanisms. Here, we sample steady-state, single-cell mRNA count distributions from parameters in the physiological range, and show that, by just comparing these distributions, estimating the number of gene states, i.e. the number of rate-limiting steps in transcriptional initiation, is unreliable. Distributions from over 99% of the parameter space generated using models with 2, 3, or 4 inactive states can be well fit by one with a single inactive state – implying that inferring more than a single inactive state is unlikely, given this approach. Instead, we show that, if the average lifetime of the mRNA is hours long, then for many minutes following induction, the increase in the mean mRNA count obeys a power law whose exponent equals the sum of the number of states visited from the initial inactive state to the active state and the number of rate-limiting post-transcriptional processing steps. We then apply standard linear regression techniques to validate the estimation of a lower bound on the number of rate-limiting steps using synthetic data. Finally, we apply non-linear regression techniques to estimate the power-law exponent and infer the number of rate-limiting steps in transcription initiation, mRNA splicing and nuclear export from eukaryotic data. Our results find genes that are consistent with the 2-state telegraph model and others that are consistent with models involving more than 2 inactive gene states.

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MATHEMATICAL MODELING OF MEASLES INFECTION DOSE RESPONSES

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The pathogenesis of viral infections is contingent upon the initial viral load upon host entry, with the nuanced implications of varying infection doses remaining incompletely understood due to practical challenges and a lack of comprehensive research. This knowledge gap is particularly pronounced in the case of the measles virus (MV), where increased infection doses exhibit a correlation with an accelerated onset of acute viremia, while the amplitude of peak viremia remains relatively constant. Measles, characterized by high transmissibility and the induction of immunosuppression leading to phenomena such as lymphopenia, poses a substantial threat to public health.

This investigation scrutinizes the intricate mechanisms governing the observed wild-type measles infection dose responses in cynomolgus monkeys. Employing the rigorous methodology of maximum likelihood estimation, longitudinal viremia data were systematically analyzed. Additionally, the Akaike Information Criterion (AIC) was employed to evaluate and refine candidate models, leading to the identification of a model suggesting a linear relationship between the infection dose, the initial viral load, and the activation of MV-specific T cells. The observed early peak in viremia is intricately associated with a heightened initial count of activated MV-specific T cells. Consequently, an elevation in MV infection dose results in an augmented early viremia and associated immune cell stimulation, thereby reducing the time for T cell-mediated viral control to be sufficient. This phenomenon allows for dose-independent peaks in viremia, MV-specific T cells, and lymphocyte depletion.

These findings underscore the critical role of virus-host interactions at the initiation of infection and the efficiency of viral control by cellular immunity in measles development. Consequently, these relationships provide additional motivation for prevention, vaccination, early diagnosis, and early treatments.

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PERIODIC OSCILLATIONS IN AN EPIDEMIC MODEL WITH LOSS OF IMMUNITY

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One of the most striking phenomena in infectious diseases dynamic is the often observed periodic or seasonal behaviour of epidemics. For instance, this is always an important issue in influenza outbreaks and recently has been crucial in trying to predict (with few success) waves of Covid-19. Although sometimes the periodic behaviour has been attributed to the seasonal influence, at least in the case of influenza, it is not well understood in general, although we note several interesting papers addressing this problem. Another extremely important issue in infectious diseases is the loss of immunity or more in general the waning immunity after being infected or vaccinated. In this talk we will present autonomous models of infectious disease dynamics, where loss of immunity is taken into account in a population structured by the age of recovery. We show by analytical means that a Hopf-bifurcation leading to periodic solutions (self-sustained oscillations) can arise, whereas a simple SIRS model cannot show such a dynamic behaviour. We also present some simple simulation results illustrating the phenomenon for different values of the parameters.

PREVALENCE OF BALANCING COMPLEXES IN LARGE-SCALE BIOCHEMICAL NETWORKS

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Constraint-based modelling of large-scale metabolic networks have identified design principles underlying metabolic functions and contributed approaches for engineering metabolic networks to improve a desired function. Success in designing engineering approaches highly depends on our understanding of the complexity of metabolic networks and dependencies among reaction fluxes imposed by the network structure. Recently, we identified two network substructures that help in understanding how network structure impacts metabolic function: (1) balanced complexes, that preserve the steady-state fluxes supported by the network [1] and (2) concordant complexes, that allow the identification of multi-reaction dependencies [2]. Here, we build up on these network structures and introduce the concept of balancing complexes. By imposing the balancing condition for a non-balanced complex in a given network, we investigate the implications on the balancing of the remaining complexes in the network. This property is quantified as the balancing potential of a complex. Using twelve genome-scale metabolic networks from organism of al kingdoms of life we found that 34% to 83% of the complexes across the analyzed networks have a non-zero balancing potential. In addition, we show that the distribution of balancing potentials follows power law distributions with exponential cut-off. Finally, we use metabolic networks of 15 cancerous and corresponding healthy tissues to demonstrate how the concept of balancing can be used in the design of intervention strategies in cancerous tissues. To this end, we identify complexes whose balancing is lethal in cancer tissue models but not for healthy tissues. Thereby, we show that the concept of balancing complexes can help in designing engineering strategies as well as in identifying new therapeutic strategies, paving new directions for usage of multi-reaction dependencies in metabolic networks.

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HIGHER-DIMENSIONAL (HD-) PARTIAL DIFFERENTIAL EQUATION (PDE) APPROACHES FOR ACUTE MYELOID LEUKAEMIA (AML)

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Acute Myeloid Leukaemia (AML) is a cancer which affects the blood and bone marrow of over 3,000 people per year in the UK, killing 2,700 per year. Though pharmaceutical and modelling efforts have been employed to combat resistance to available treatments for AML, resistance remains a persistent barrier to recovery. In recent years, higher-dimensional partial differential equation (HD-PDE) models have been successfully used to simultaneously characterise biochemical and spatio-temporal heterogeneity, in the systematic emergence of resistance to targeted treatments in solid tumours. Through this work, we utilise HD-PDEs in an effort to characterise the bio-temporal heterogeneity arising during the treatment of AML, and to attempt the identification of subgroups which may respond more favourably to particular treatments, a priori. I will present novel approaches to dimensional reduction in HD-PDE methods; a derivation for bottom-up modelling of AML; alongside preliminary results which indicate successes of the approach and possible future directions.

MATHEMATICAL INSIGHTS INTO CYCLIC MULTIDRUG THERAPY: HOW TEMPORALLY HETEROGENEOUS TREATMENTS CAN CONTROL PHENOTYPICALLY HETEROGENEOUS TUMOUR

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Adaptive therapy aims to control cancer resistance by combining different drugs and treatment regimens. It uses evolutionary concepts such as resistance cost and competitive release to introduce strategies that exploit remaining sensitive cancer cells to suppress less competitive resistant cells [1]. We present mathematical results establishing the existence of a successful adaptive multi-drug treatment described by a Lotka-Volterra system with periodic coefficients, n competing phenotypes of tumor cells, and m different drugs applied cyclically over time. Adapting a result of Xia [2], we provide conditions on parameters under which the model has a globally attracting limit cycle, representing cyclic tumor dynamics that avoids the growth of resistant cells. Focusing on the two- and three-dimensional cases and using Zeeman's classification of Lotka-Volterra systems [3], we show that an attracting limit cycle exists when the mean autonomous system associated with the periodic system has an internal coexistence equilibrium; the coefficients of the mean autonomous system are the average of the periodic coefficients. In other words, while single-drug treatments usually select for resistant phenotypes, a cyclic multi-drug treatment can trap the dynamics of tumor cells in periodic oscillations if it is applied in such a way that its virtual mean effect leads to the coexistence of phenotypes. We show that the patient-specific conditions required for such a treatment can be satisfied by correctly mixing the dosage and timing of the different drugs, and illustrate our conclusions with patient parameters from the literature. In conclusion, our results provide mechanistic insights into the design of successful cyclic multidrug treatment strategies and contribute to the growing view that the treatment of refractory cancers should be based on both interpatient and intratumoral heterogeneity and aim to delay or control tumor progression rather than to kill as much as possible.

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FEEDBACK-FORWARD CONTROL IN SINGNALLING PATHWAYS

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Analysis of cellular signalling pathways and development of their mathematical models is one of the main interests of mathematical biology. Positive and negative feedback loops are well-established concepts in such analysis. However control theory, and engineering experience show that more advanced structures are viable options in many problems [1]. The complexity of biological interactions suggests that more complex control structures may be found in their models.

One of the most basic structures, used widely in industrial applications, is a feedback-feedforward structure, which joins benefits of standard feedback control with feedforward ability to quickly react to disturbances in the system. It includes two controllers, one responsible for standard feedback reaction and the second for filtering the input signal and directly supplying it to the plant.

As a basis for the talk, selected signalling pathways were analysed in order to locate biological analogues to technical feedback-feedforward loop. Analysis involved construction of block diagrams representing pathway's model's equations, transformations of those diagrams in order to find and emphasise the presence of searched structures. Several pathways were taken into consideration e.g. p53/Mdm2 [2] or pathway related to epithelial-mesenchymal transition [3]. Models for selected pathways were taken from the literature, with a limitation that models should be based on ODEs, and consist no more than 10 of them.

In the talk, conclusions arising from additional control structure in the model will be discussed, together with possible new targets for external influence on the pathway.

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AN INTERPRETABLE PREDICTION METHOD FOR ANTIBODY BINDING AFFINITY BASED ON MATHEMATICAL MODELS OF STRUCTURAL FLUCTUATIONS AND DEEP LEARNING

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The high binding affinity of antibodies towards their cognate targets is key to eliciting effective immune responses, as well as to the use of antibodies as research and therapeutic tools. Here, we propose a Convolutional Neural Network model (called ANTIPASTI) that achieves state-of-the-art performance in the prediction of antibody binding affinity.

The key novelty of our method is that it takes as input a representation of antibody structures that relies on a coarse-grained mathematical model of the antibody-target bound complex as an elastic network of residues. This model uses spectral descriptions to capture energetic patterns of local and global residue fluctuations upon target binding, allowing us to obtain an input representation of antibodies in terms of correlations between molecular fluctuations across their structure. Thanks to this modelling choice, our method harnesses the dynamical information encoded in the residue-residue connectivity pattern of antibody-target complexes for the numerical prediction of binding affinity, with a prediction performance that compares favourably to existing machine learning methods.

Furthermore, the internal representations learnt by the neural network and leveraged for prediction prove to be biophysically interpretable: they reveal similarities of binding patterns among antibodies binding to the same target type, and can be used to quantify the importance of antibody regions contributing to binding affinity. Our results highlight the dominance of cooperative effects and long-range correlations between antibody regions to determine binding affinity, and the comparison to experiments of site-directed mutagenesis in antibodies corroborates these observations by yielding plausible mechanistic interpretations of such effects. Hence, our approach provides predictions and biophysical insights that can help identify targets for the laboratory-controlled evolution of antibodies with increased binding affinity.

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AMPLITUDE AND FREQUENCY VARIATION IN STIMULATED GLYCEMIC RHYTHMS

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The glycemic response to a glucose stimulus is an essential tool for detecting deficiencies in humans such as diabetes. In the presence of constant and periodic glucose infusions in healthy individuals, it is known that this control leads to slow oscillations as a result of feedback mechanisms at the organ and tissue level. These ultradian oscillations are typically modelled using systems of nonlinear equations with two discrete delays and here we give a particular attention to its periodic solutions. These arise from a Hopf bifurcation which is induced by an external glucose stimulus and the joint contributions of delays in pancreatic insulin release and hepatic glycogenesis. The effect of each physiological subsystem on the amplitude and period of the oscillations is exhibited by performing a perturbative analysis of its periodic solutions. It is shown that assuming the commensurateness of delays enables the Hopf bifurcation curve to be characterised by studying roots of linear combinations of Chebyshev polynomials. The impact of periodic (sinusoidal and on-off) infusions is characterised through numerical bifurcation analysis. The resulting expressions provide an invaluable tool for studying the interplay between physiological functions and delays in producing an oscillatory regime, as well as relevant information for glycemic control strategies.

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MODELLING THE IMPACT OF MASS GATHERING EVENTS (MGE) ON POTENTIAL FUTURE PANDEMICS

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To assess the potential effects of mass gathering events (MGE) on a potential new pandemic outbreak, we adapt an individual-based model developed for SARS-CoV2. We investigate both direct and indirect (secondary cases) effects of MGE by varying the conditions regarding the MGE itself as well as control measures in society. MGE conditions include size, participant density and ventilation. Prevention measures during MGE include mask wearing and prior testing. Control measures outside the MGE include contact tracing with possible succeeding quarantine as well as general contact reduction. Apart from the MGE itself, person-to-person contacts can take place in one of the following settings: own household, school/workplace, leisure. The number of contacts in the settings is based either on POLYMOD or COVIMOD studies on social mixing patterns. We model the disease stages using an extended Susceptible-Exposed-Infected-Recovered model. In addition, the model incorporates age-specific severity of disease, as well as prior immunity. Infection probability and disease progression parameters are based on data from SARS-CoV2 as the current most detailed source of respiratory infections. These parameters are varied in sensitivity analyses. Generally, the results of the study show little impact of MGE unless very unfavourable assumptions, especially regarding aerosol transmission are used.

SPEED AND SHAPE OF POPULATION FRONTS WITH DENSITY DEPENDENT DIFFUSION

Beth Stokes (University of Bath)
Other authors: R. James, T. Rogers

Understanding how and why animal populations disperse is a key question in movement ecology. There are many reasons for dispersal, such as overcrowding and searching for food, territory or potential mates. These behaviours are often dependent on the local density of the population. Motivated by this, we investigate an FKPP equation with density dependent diffusion. Using a combination of linear stability analysis and variational arguments, we derive bounds on the minimum realisable wavespeed of travelling wave solutions for different diffusion functions. We find that the linear stability analysis suggests that the is entirely determined by diffusion at zero density, regardless of how the function behaves on the rest of the domain. Applying the variational arguments, we then see how the selected wavespeed may differ from this, depending in more detail on the diffusion profile across all densities. We explore the system dynamics across both discrete and continuous domains, and present results for the wavespeed and shape of travelling wave fronts with diffusion functions describing a variety of cases of both positive and negative density dependence.

THE REPRODUCTION NUMBER AND ITS PROBABILITY DISTRIBUTION FOR STOCHASTIC VIRAL DYNAMICS

Bevelynn Williams (University of Leeds)
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We will analyse stochastic models of within-host viral infection dynamics, derived from deterministic equations. These models consider an eclipse phase: the period of time after a cell is infected but before it is capable of releasing virions. The duration of the eclipse, or the subsequent infectious, phase is non-exponential, but composed of stages. The basic reproduction number, R, is understood as a random variable representing the number of new cells infected by one initial infected cell in an otherwise susceptible (target cell) population. Variability in R results partly from heterogeneity in the viral burst size (the number of viral progeny generated from an infected cell during its lifetime), which depends on the distribution of cellular lifetimes and on the mechanism of virion release. We will derive the probability distributions of the burst size and the reproduction number for these viral dynamics models, and will see that these are negative binomial distributions in the case of gamma-distributed infectious periods, and under the assumption of an excess of target cells. In a deterministic model, the ultimate in-host establishment or extinction of the viral infection depends entirely on whether the mean reproduction number is greater than, or less than, one, respectively. In the stochastic models presented here, the probability of extinction is determined by the whole probability distribution of R, not simply its mean value. In particular, we will see an example in which the probability of extinction is not a decreasing function of the mean reproduction number. Through numerical examples, it will be shown that distributional assumptions on the eclipse and infectious periods matter, as well as the amount of target cells at the infection site. Furthermore, the role played by the early immune response can be significant in specific scenarios.

QUANTIFYING OPTIMAL RESOURCE ALLOCATION STRATEGIES FOR CONTROLLING EPIDEMICS

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Frequent emergence of communicable diseases is a major concern worldwide. Lack of sufficient resources to mitigate the disease burden makes the situation even more challenging for lower-income countries. Hence, strategy development for disease eradication and optimal management of the social and economic burden has garnered a lot of attention in recent years. In this context, we quantify the optimal fraction of resources that can be allocated to two major intervention measures, namely reduction of disease transmission and improvement of healthcare infrastructure. Our results demonstrate that the effectiveness of each of the interventions has a significant impact on the optimal resource allocation in both long-term disease dynamics and outbreak scenarios. The optimal allocation strategy for long-term dynamics exhibits non-monotonic behavior with respect to the effectiveness of interventions, which differs from the more intuitive strategy recommended in the case of outbreaks. Further, our results indicate that the relationship between investment in interventions and the corresponding increase in patient recovery rate or decrease in disease transmission rate plays a decisive role in determining optimal strategies. Intervention programs with decreasing returns promote the necessity for resource sharing. Our study provides fundamental insights into determining the best response strategy when controlling epidemics in resource-constrained situations.

COMPUTING THE DYNAMICS OF MOTILE BACTERIA USING A CALIBRATED NUMERICAL MODEL

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Other authors: K.M. Brown, J. McCoy, R. Cortez, A. Gibbs, F. Healy, H. Nguyen, O. Shindell

The Trinity-Centre Collaboration uses dynamically similar table-top experiments to test theories for objects such as cylinders, spheres, and helices moving in Stokes flow near a boundary. We then use these data to calibrate the Method of Images for Regularized Stokeslets (MIRS) for use as a noninvasive probe of bacterial swimming dynamics. We have previously calibrated the MIRS for rod shaped cylindrical bodies but have extended the work by verifying for the first time the theoretical predictions by Lee and Leal (1981) for the forces and torques on spheres moving near boundaries. Bacterial trajectories measured using TIRF microscopy are characterized using our new tracking scheme to yield the body orientation and boundary distance of the bacteria. The trajectories are inputs into the MIRS from which forces and torques are computed to better understand how these microorganisms swim and how efficiency measures are affected by body and flagellar geometries. See the accompanying talk by Hoa Nguyen to see how the MIRS is calibrated.

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EVOLUTIONARY GENERATION AND OPTIMALITY OF SOCIAL CONTACT NETWORKS

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Contacts between individuals effectively bring many benefits, such as opportunities for collaboration, but these also play an important role in spreading infectious diseases. Widespread infection also sometimes causes a reduction in the amount of physically close contacts in a community. This will lose opportunities, e.g. for cooperation, that might otherwise be achieved as a consequence. Here, we propose and analyse a novel simplified network SIS model using Kirkwood and maximum entropy moment closure principles. This talk will present our analysis, which gives an analytical result for the prevalence of infection at endemic equilibrium and its basic reproduction ratio (R0). This allows us to illustrate the relationship between the expected number of links for each individual and the endemic number of infected individuals, comparing those of the mean-field approximation model and the pairwise model. This project will then attempt to present an analysis of the trade-off between social contact benefits and the risk of getting an infection.

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OPTIMAL CONTROL OF TUMOUR GROWTH TO MAXIMIZE PATIENT LIFE EXPECTANCY

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We propose a novel optimal control theory (OCT) formulation that evaluates the efficacy of cancer-chemotherapy treatments in terms of the patient's expected lifetime and possible cancer futures/outcomes, such as tumor clearance, tumor relapse and death due to treatment. All parameters have direct biological interpretations; thus, the proposed formulation could be potentially used in the development of personalized treatments (provided that individual risk can be determined). Our model is based on a deterministic OCT framework; however, we have taken into account stochastic effects such as cancer cell lineage die out. In the first part of the talk, we present the formulation in a general/theoretical setting. Individual characteristics, such as patient age and the susceptibility of the patient to chemotherapy induced adverse drug reactions, are considered. We find that optimal solutions are Bang-Bang and have either no switch or a single switch giving solutions that are (i) continuous treatment at maximum tolerated dose (MTD), (ii) no treatment or (iii) treat-and-stop solutions, treating at MTD and stopping drug administration before the time horizon is reached. Optimizing over the time horizon, treatments are either 'no treatment', i.e. patients are untreatable since there is no benefit under treatment, or MTD for a specified time. Patients thus split into an untreatable class and a treatable class, with patient demographics, tumor size, tumor response and drug toxicity determining a patient's benefit under treatment. In the second part of the talk, we discuss applications of the OCT formulation in the context of chemotherapy treatments for acute myeloid leukemia. A hematopoietic model is employed to describe the differentiation and maturation of healthy and leukemic cells and a pharmacodynamic model expresses drug induced myellosuppression. Drug regiments are restricted to keep the absolute neutrophil count larger than a basal level.

LEARNING A CANCER'S EVOLUTIONARY HISTORY FROM BULK METHYLATION DATA USING BAYESIAN INFERENCE.

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Evolution underlies the transformation of a normal cell to a cancer, yet learning the parameters defining this dynamic process from single-timepoint bulk samples is an open challenge. However, the evolutionary history of a cancer is hidden within the patterns of heritable changes within its constituent cells. Here, we identified specific methylation sites within the genome that function as natural molecular clocks in lymphoid cancers. Combining these clocks with a stochastic model of cancer growth allowed us to infer the evolutionary histories of 1976 lymphoid cancers using Bayesian methods. Remarkably, the inferred evolutionary parameters were strongly predictive of future disease outcome.

In our previous work, we discovered fluctuating CpGs (fCpGs) [1], which neutrally and stochastically change methylation state over time in vivo, uniquely barcoding cells and thus enabling high temporal-resolution lineage tracing. For the current study, we developed a stochastic model describing how the patterns of fCpGs varied with the cancer growth dynamics and a pseudo-likelihood Bayesian inference method to infer these parameters from data, which we termed EVO-FLUx [2].

Applying EVO-FLUx to a cohort of 1976 lymphoid samples spanning a broad range of cancer types, we demonstrated that tumour growth rates and malignancy ages differed by orders of magnitude. In 2 independent cohorts of chronic lymphocytic leukaemia (CLL) patients the inferred growth rates were highly prognostic.

The presence of an expanding subclone could be detected by employing leave-one-out cross validation as a model selection method, which we validated using orthogonal genetic data. Similarly, the evolutionary relationship between longitudinal samples was characterised using fCpGs and validated using matched deep whole genome sequencing data.

Hence, we have developed a powerful and generalisable tool to learn the evolutionary history of cells in vivo in a scalable, clinically-relevant manner.

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EFFICIENT COUPLING OF WITHIN- AND BETWEEN-HOST INFECTIOUS DISEASE DYNAMICS

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Mathematical models of infectious disease transmission typically neglect within-host dynamics. Yet within-host dynamics – including pathogen replication, host immune responses, and interactions with microbiota – are crucial not only for determining the progression of disease at the individual level, but also for driving within-host evolution and onwards transmission, and therefore shape dynamics at the population level. Various approaches have been proposed to model both within- and between-host dynamics, but these typically require considerable simplifying assumptions to couple processes at contrasting scales (e.g., the within-host dynamics quickly reach a steady state) or are computationally intensive. Here we propose a novel, readily adaptable and broadly applicable method for modelling both within- and between-host processes which can fully couple dynamics across scales and is both realistic and computationally efficient. By individually tracking the deterministic within-host dynamics of infected individuals, and stochastically coupling these to continuous host state variables at the population-level, we take advantage of fast numerical methods at both scales while still capturing individual transient within-host dynamics and stochasticity in transmission between hosts. Our approach closely agrees with full stochastic individual-based simulations and is especially useful when the within-host dynamics do not rapidly reach a steady state or over longer timescales to track pathogen evolution. By applying our method to different pathogen growth scenarios we show how common simplifying assumptions fundamentally change epidemiological and evolutionary dynamics.

MULTICOMPONENT FRAGMENTATION AND COAGULATION IN POLYMER-BACTERIAL CLUSTERING

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Antimicrobial resistant bacteria is one of the biggest threats to public health today. Resistant bacteria already account for more than 750,000 global fatalities annually – a figure that has been predicted to rise to upwards of 10 million individuals by the year 2050 if effective interventions are not implemented. It is critical that novel treatment strategies are developed to counteract such a hazard to human and animal life, either to replace or be used in tandem with existing antimicrobials. One such treatment is an antimicrobial polymer, which has the potential to inhibit adhesion (a necessary step for biofilm formation) and to modulate quorum sensing controlled virulence.

In this work, we focus on polymers that can promote bacterial clustering, thus inhibiting their ability to bind to host cells and deploy virulence factors. We utilise a modification of the discrete multicomponent coagulation-fragmentation ODE model to capture polymer and bacterial clustering. At present our experimental data can tell us the distribution of cluster sizes in the long-term, but does not allow us to unpick the trajectory taken to arrive there - something which is important to understand if these polymers are to be exploited for treatments. By comparing our model against experimental data (and performing parameterisation where possible), our mathematical analysis focuses on elucidating the underlying mechanisms and time courses of cluster formation. .

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NUMERICAL SCHEMES FOR SIR MODEL

Canan Akkoyunlu (Istanbul Kultur University)

Mathematics has played very important role in humanity because of modelling and simulation for infectious diseases. The spread of infectious diseases can be modelled and simulated. The SIR model is the most popular epidemic model with three populations, the susceptible group S, infectious group I, and recovered group R. It characterizes infectious diseases that provide immunity upon infection. Unfourtunately, the SIR model does not have an analytical solution for the time course of its populations. A numerical solution for SIR model was done by the use of the implicit scheme for different parameters.

ANTICIPATING PATHOGEN DYNAMICS USING BAYESIAN MODEL-AVERAGING WITH PARTIAL DIFFERENTIAL EQUATIONS

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Anticipating the dynamics of invasive pathogens is crucial for devising effective eradication and containment strategies. Utilizing a model based on partial differential equations (PDE), commonly employed for invasion modeling, and calibrated with surveillance data facilitates the creation of concise yet mechanistically grounded models incorporating real-world observations. However, reliance on a single PDE-based model may result in overly rigid behavior and potential mismatches with data. To mitigate this, we propose the application of Bayesian model averaging (BMA), addressing both parameter and model uncertainties. Our approach involves generating a set of competing PDE-based models to represent pathogen dynamics, utilizing an adaptive multiple importance sampling algorithm (AMIS) for parameter estimation, evaluating posterior model probabilities through comparison methods from the literature, and applying BMA to derive posterior distributions of parameters and forecast pathogen dynamics. We implement this methodology to predict the spread of Xylella fastidiosa in South Corsica, France, a phytopathogenic bacterium detected in Europe less than a decade ago (Italy 2013, France 2015). Through the separation of data into training and validation sets, we demonstrate the superior performance of BMA forecasting compared to alternative approaches.

QUANTIFYING CYTOSKELETAL DYNAMICS AND REMODELING FROM LIVE-IMAGING MICROSCOPY DATA

Carey Li (University of St Andrews)

The shape of biological cells emerges from dynamic remodeling of the cell's internal scaffolding, the cytoskeleton. Hence, correct cytoskeletal regulation is crucial for the control of cell behaviour, such as cell division and migration. A main component of the cytoskeleton is actin. Interlinked actin filaments span the body of the cell and contribute to a cell's stiffness. The molecular motor myosin can induce constriction of the cell by moving actin filaments against each other. Capturing and quantifying these interactions between myosin and actin in living cells is an ongoing challenge. For example, live-imaging microscopy can be used to study the dynamic changes of actin and myosin density in deforming cells. These imaging data can be quantified using Optical Flow algorithms, which locally assign velocities of cytoskeletal movement to the data. Extended Optical Flow algorithms also quantify actin polymerization and depolymerization. However, these measurements on cytoskeletal dynamics may be influenced by noise in the image acquisition, by ad-hoc parameter choices in the algorithm, and by image pre-processing steps. Here, we use in silico data to understand conditions under which Optical Flow is applicable. The development of our Optical Flow method will be a starting point for identifying differences in cytoskeletal movement and remodeling under experimental perturbations.

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MEASURING THE COST-EFFECTIVENESS OF COVID-19 VACCINATION: A MODELLING STUDY

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Vaccination has played a vital role in mitigating the impact of the COVID- 19 pandemic. In this presentation, we will share the results of a retrospective analysis examining the effectiveness of the initial phase of COVID-19 vaccination in the Basque Country, spanning January to December 2021. Employing a deterministic framework, we describe several phases of COVID-19 dynamics in the Basque Country, incorporating estimates of biological parameters such as transmission and mortality rates during the one-year vaccination rollout. Our model is calibrated using real-world data on hospitalizations, Intensive Care Unit (ICU) admissions, and deaths. We compare the results with a scenario without vaccination to calculate the quality of life years (QALYs) preserved due to vaccination. Subsequently, we consider the costs related to infection, vaccination, hospitalization, and ICU admission to assess the incremental cost-effectiveness ratio (ICER) from the healthcare system's perspective. This ratio, expressed in euros per QALY gained, is a commonly used metric in decision-making for resource allocation.

INFERENCE ON NATURAL SELECTION FOR A FAMILY OF WRIGHT-FISHER DIFFUSION MODELS

Celia García Pareja (KTH Royal Institute of Technology)
Other authors: F. Nobile

In this talk, our interest lies on inferring the selective advantage of a newly appeared mutant with respect to the wild-type in a well-mixed population. This is of great importance in applications where the question is whether a newly appeared mutation is likely to sweep over the population. Think, for instance, in seasonal flu vaccine planning, where the goal is to predict the most prevalent genetic variant a year ahead of time, so that effective vaccines can be designed before the next season. In our work, the evolution of mutant frequencies is described according to a one-dimensional Wright-Fisher diffusion model. Given an observed evolutionary trajectory of the frequency of mutants, we present an unbiased Monte Carlo maximum likelihood estimator for the selection parameter of a discretely observed Wright-Fisher diffusion. Our estimation approach is based on exact simulation techniques that are of special interest for diffusion processes defined on a bounded domain, where numerical methods typically fail to remain within the required boundaries. I will mention how our method extends to the multidimensional case, where one can simultaneously consider the evolution of several mutant strains and infer their selective advantages. Consistency results of our proposed estimator are also presented and the performance of our method will be illustrated through numerical examples.

EVALUATING THE POTENTIAL OF MICROSPORIDIA MB (MB) SYMBIONT IN MALARIA CONTROL USING MATHEMATICAL MODELLING.

Charlene N. T. Mfangnia (University of Dschang)
Other authors: Henri E. Z. Tonnang, Berge Tsanou, Jeremy Herren

Microsporidia, an endosymbiont present in Anopheles mosquitoes, has the Plasmodium-transmission blocking property. Thus, spreading this endosymbiont in the anopheline population, could contribute to malaria control. In this work, we develop a mathematical model to analyze the feasibility of malaria control using the symbiont MB. The first point is reproducing the dynamics of MB-infected mosquitoes as observed from field data. The second objective is to predict the effect of an increase prevalence of MB-infected mosquitoes on malaria incidence. The third and last objective is to design optimal release programs to strategically increase the prevalence of MB-infected mosquitoes. Through analytical computations, we provide the conditions for extinction and persistence of MB-infected mosquitoes, extinction and persistence of malaria in humans in presence or absence of MB-infected mosquitoes. This is done through the analysis of the local and global stability of the equilibria. In addition, through numerical analysis, we observe that, a low prevalence of MB-infected mosquitoes, as reported from field experiments is associated to a low horizontal transmission efficiency of the symbiont during the mating event in the vector population. Then, we predict and map in Kenya, according to a given initial malaria prevalence of malaria, the impact of an increased prevalence of MB-infected mosquitoes, on malaria incidence. The effects of the seasonality, together with the difference in the malaria dynamics across regions, reinforces the necessity of targeted interventions for malaria control. Finally, we provide some impulse release strategies, to increase the prevalence of MB-infected mosquitoes and therefore, reduce malaria incidence in the field. This study serves to guide experiment on the field for malaria control using the Microsporidia MB symbiont.

TRACTABILITY CHALLENGES FOR BIOCHEMICAL NETWORK MODELS

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Other authors: Robyn Araujo, Lan Nguyen, and Mark Flegg

Biochemical networks are often depicted mathematically using nonlinear coupled Ordinary Differential Equations (ODEs). However, gaining general insight into the behaviour of these models using classical analysis methods can be challenging due to their high dimensionality and nonlinearity and general intractability. Understanding biochemical networks often takes a qualitative direction. Some specific behaviours, such as oscillation, are commonly associated with prevalent network features (for example, identifiable negative feedback can often explain oscillatory behaviour). This raises the question of the mathematical equivalency of models of qualitative features. For example, if Gene A promotes Gene B which promotes Gene A, then this is an example of positive feedback, but does this behave in the same way as Gene A inhibits Gene B which inhibits Gene A? The answer obviously lies in the quantitative nature of the mathematical model. It is therefore important to understand what properties of the mathematical model permit approximating of these systems as the same and if this is the case, would it be possible to reduce biochemical networks into a simpler oriented (canonical) form? We will explore these questions in this talk.

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MATHEMATICAL MODELING OF PLATELET FORMATION IN HEALTHY INDIVIDUALS AND BLOOD CANCER PATIENTS

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Platelets are derived from multipotent hematopoietic (blood forming) stem cells, which give rise to all mature blood cell types. To counteract bleeding and thrombosis, platelet formation is tightly regulated by non-linear feedback mechanisms. Platelet formation is perturbed in many clinical contexts such as excessive blood loss, bone marrow transplantation and blood cancers. An example for the latter are the so-called myeloproliferative neoplasms (MPNs), a heterogeneous group of slowly progressing blood cancers. MPN patients harbor a malignant stem cell population which carries specific mutations (e.g. in JAK2, CALR or MPL gene) and triggers an increased formation of mature blood cells. Patients often suffer from a high comorbidity burden including cardiovascular events and thrombosis. A detailed understanding of platelet formation and its dynamics is of high clinical importance. In this study, we propose a set of quantitative ordinary differential equation (ODE) models to elucidate the formation of platelets in individuals with and without MPNs. The proposed models account for multiple types of immature cells which contribute to platelet formation. Mature and immature cell dynamics are regulated by a non-linear feedback mechanisms modeling thrombopoietin (TPO), the major modulator of thrombopoiesis. We parameterize the model in absence of malignant mutations using blood cell counts in patients who underwent bone marrow transplantation. Systematic comparisons of different candidate models reveal which TPO effects are necessary for a quick recovery of platelet counts and which cellular processes could be targeted to boost platelet formation. We extend the model to MPN by including a mutated cell lineage and simulate system dynamics assuming alterations of key cell parameters. By systematically exploring the effects of these changes, we aim to identify critical factors leading to dysregulated thrombopoiesis in MPN patients and to disease progression.

CONTROL OF STOCHASTIC BIOCHEMICAL OSCILLATORS: FEEDBACK STABILIZATION AROUND THE LOW PROBABILITY REGION

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Gene regulation is a fundamental process in cell biology, and understanding and controlling the dynamics of genetic regulatory circuits is one of the goals of synthetic biology. Gene regulation is an inherently stochastic process, and current literature emphasizes the need of taking molecular noise into account on the design and control of biocircuits to improve their performance in realistic scenarios [1].

In this work, we apply control to stochastic gene regulatory networks, based on the partial integro-differential equations (PIDE) model developed by [2], which provides an efficient approximation to the stochastic dynamics of GRNs, avoiding the unmanageable complexity associated with the Chemical Master Equation.

Specifically, we address the problem of stabilizing stochastic biochemical oscillators around their low probability region (corresponding to unstable focus of the limit cycle oscillator at the deterministic limit). For this purpose, we developed a Proportional-Integral Adaptive control strategy, which has been already proven to be effective in the stabilization and suppression of oscillations in the deterministic regime. In order to illustrate the effectiveness of the method proposed we have chosen as a case study the first synthetic oscillator implemented in bacterial cells, the Repressilator by [3].

The results obtained demonstrate the effectiveness of the proposed approach based on PIDE and Adaptive PI control for suppressing oscillations and stabilizing the system around its low probability region, providing a theoretical and computational framework towards precise control of the dynamics in gene regulatory networks.

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A MODEL FRAMEWORK FOR CALCIUM ION CHANNELS: CONSISTENT MODELING OF SELECTIVITY FILTERS

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Calcium ion channels play an important role in various cellular processes, including muscle contraction and the release of neurotransmitters. The preferential passage of calcium ions over other ions in these pores is regulated by an important structural element, the selectivity filter. Size and shape of this element determine which ions are allowed to pass. In addition, electrostatic forces coordinate and stabilize the ion flow. Ion selectivity controls various cellular processes, and channelopathies have been linked to mutations within the filter region. A sophisticated understanding of the selectivity filter therefore holds potential for the development of new drugs and therapeutic strategies. We aim to formulate a model framework that facilitates the interpretation of experimentally measured data, in particular current-voltage relations. The foundation of our model is based on non-equilibrium thermodynamics, which accounts for finite-size effects, solvation phenomena and charges on the membrane and channel proteins. We place particular emphasis on consistent modeling of the selectivity filter and treat it as an additional embedded domain in which the constituents can change their chemical properties. The diffusion process through the filter is determined by an independent diffusion coefficient, and de- and resolvation reactions are introduced at the interfaces as Neumann interface conditions. The framework enables the calculation of current-voltage relations across a spectrum of channel properties and ion concentrations. The resulting continuum model is solved in Julia using the Voronoi finite volume method. A comparison with experimental results for calcium-selective ion channels demonstrates the validity of our approach.

HOW POLARISATION AND DEPOLARISATION AFFECTS THE SPREADING OF MIGRATING CELLS

Christophe Deroulers (Université Paris Cité)

Predicting the spatial distribution of migrating living cells is interesting, if not compulsory, in many circumstances, e.g. development, growth, wound healing, cancerous expansion, metastases. In particular, in the case of the brain tumours called diffuse gliomas, one needs to compute reliably where, in the brain, tumour cells have infiltrated the parenchyma, as a function of time.

Indeed, these cells are believed to be the cause of recurrences of the disease after treatment (surgery, radiotherapy, chemotherapy), thus of the poor diagnosis. Yet routine imaging like MRI is unable to detect them because their concentration is too low, leaving theoretical models as a promising alternative approach. It could help guide the existing treatments, and design new treatments, by simulating the effects of the modification of biological parameters of individual cells (e.g. by drugs) on the spreading at the scale of the organ.

In this work, we extend previous models of cell migration to incorporate the so-called cell polarisation and study its effects. We find that this switching of cells between a motile state, with a roughly conserved direction of motion and a strongly elongated shape, and a depolarised non-motile state with a more compact, rounded shape, has strong and surprising consequences at the macroscopic scale of the full population spreading when cell density is not low, even though it concerns initially only individual cells.

Due to the high number of cells at the scale of the organ (almost one billion), a continuum model like a partial differential equation is most tractable. However, there is no obvious such model based on the behaviour of cells at the microscopic scale. Thus we build an approximate one, using a combination of Monte Carlo simulations and analytic techniques like hydrodynamic limits. We believe that our findings can apply more generally to non tumorous migrating cells.

MODELLING IMMUNE CELL-ENDOMETRIAL CELL DYNAMICS IN ENDOMETRIOSIS

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Endometriosis is a chronic gynaecological condition affecting around one in nine people with a uterus. The disease is characterised by the growth of lesions of endometrial-like cells outside of the uterus, such as in the peritoneum (lining of the abdomen and pelvis). Symptoms include chronic pain and fertility issues. The hypothesised root cause of endometriosis is retrograde menstruation—where menstrual debris is ejected through the fallopian tubes and into the peritoneal cavity rather than out the cervix. However, the cause must be more complex than this as retrograde menstruation is more common than endometriosis.

The pathophysiology of endometriosis closely resembles that of cancer, with abnormal cell growth and angiogenesis to support lesion growth. Like cancer, a hypothesised factor in disease onset is the local immune system which not only fails to eliminate ectopic cells, but potentially aids lesion formation [1]. Supporting this hypothesis, abnormal immune profiles have been observed in peritoneal fluid of endometriosis patients [2]. This raises the question as to whether these abnormal profiles are due to an abnormal immune response to the endometrial cells, or simply due to a consistent presence of endometrial cells in the peritoneal cavity.

We have developed a population dynamics model for immune cell response to endometrial cells in peritoneal fluid, inspired by previous models of immune cell responses to cancer and viral attack. Altered macrophage and natural killer cell behaviours are commonly implicated in endometriosis in the literature [3]. Consequently, we focus on these cell types in the model, which are each expressed with three activation states.

Using this model, we determine the parameter regimes under which endometrial cells do or do not persist as lesions. In particular, those related to three hypotheses that could contribute to altered immune profiles: immune escape, decreased immune cell efficacy, and increased endometrial cell reflux.

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HYPOXIA-INDUCIBLE FACTORS (HIFS) AND OXYGEN HOMEOSTASIS: THE MAKING OF A (MISLEADING) BIOLOGICAL THEORY

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The discovery of Hypoxia-inducible factors (HIFs), awarded the Nobel Prize in 2019, constituted a groundbreaking milestone in our understanding of the molecular mechanisms enabling cells to sense and adapt to oxygen availability. HIFs regulate the expression of genes involved in primary metabolic pathways such as glycolysis, fermentation, or the TCA cycle. Moreover, their activity is residual in cells under normoxia (20% oxygen), and increases exponentially in cells exposed to hypoxia (1% oxygen). These observations laid the foundation of the prevailing paradigm of intracellular oxygen homeostasis: HIFs orchestrate a cellular response to hypoxia, promoting the use of anaerobic pathways of energy generation when oxygen becomes a limiting factor. In this presentation, we suggest that this view of oxygen homeostasis has critical limitations and provides a profoundly misleading picture of HIFs function. We argue that this explanation lacks an appropriate physiological context, and formulate an alternative conceptual model of the interplay of HIFs regulation with primary pathways of energy generation in the cell. A mathematical translation of this model suggests that HIFs do not coordinate a cellular stress response but prevent the onset of hypoxic stress in the first place. The explanatory power of our approach is patent in its interpretation of the Warburg effect (WE). The WE is the tendency of cancer cells to favor anaerobic metabolism over aerobic respiration, even in fully aerobic conditions. This puzzling metabolic choice, together with HIFs upregulation is currently considered a hallmark of tumor cells and an aberrant deviation of healthy cellular metabolism. According to our model, the shift toward anaerobic metabolism in tumor cells would be the expected consequence of HIFs upregulation, which in turn would be the expected homeostatic response to the abnormal increase in metabolic demand that characterizes malignant phenotypes.

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INTER-SPECIES PATHOGEN TRANSMISSION USING STOCHASTIC MODELS WITH DEMOGRAPHICS: APPLICATIONS IN AQUATIC ECOSYSTEMS

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Aquatic ecosystems are diverse and complex environments that support a wide range of life forms, including pathogens such as viruses. These pathogens play a significant role in the overall biomass of these ecosystems. The presence of numerous pathogens, especially those capable of infecting fish species, highlights the dynamic nature of aquatic ecosystems. With climate change causing shifts in fish species' ranges, formerly non-overlapping ranges are now intersecting. This transition leads to increased encounters between species that were previously infrequent or nonexistent. This has important implications for the propagation of pathogens within these changing ecological contexts. To understand the complex dynamics of pathogen propagation in this changing ecological context, this study utilizes continuous-time Markov chains (CTMC) for the propagation of V virus inside P species of fish. CTMC modeling framework is employed to represent both the stochastic and temporal components of pathogen propagation. We used branching process approximation to compute the probability of a disease outbreak, denoted as Pob. When the basic reproduction number, R0, is less than one, Pob is equal to zero. However, when R0 is greater than one, 0 ¡ Pob ¡ 1. The specific case of the propagation of the Infectious Hematopoietic Necrosis (IHN) to Sockeye Salmon and Chum Salmon is presented as an example. A sensitivity analysis of the probability of INH outbreak reveals that natural birth rates, incubation rates, and mortality rates significantly influence, compared to other parameters, the spread of IHN.

NONLOCALITY-INDUCED INSTABILITIES IN REACTION DIFFUSION SYSTEMS ARISING FROM MODELING INFLAMMATION

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Modeling inflammatory processes motivates reaction-diffusion models with nonlocal and heterogeneous reaction terms. There, the nonlocality describes abstracted signaling and production processes leading to an increase of immune cells in the tissue. In this application, the parameter for the nonlocality may change the dynamics from persisting inflammation to vanishing inflammation.

More generally, the parameters of the nonlocal terms influence the stability of stationary states from stable behavior to instability. Starting from stable reaction diffusion equations without nonlocality, I present results on instabilities induced by a heterogeneous nonlocal term in the reaction functions. The introduction of nonlocality in the reaction functions poses new challenges: Linearizing the nonlocal system leads to a strongly coupled infinite-dimensional system of ordinary differential equations for the eigenmodes. We show that the infinite dimensional linear system can be approximated by a truncated system. A combination of analytical and numerical results for the nonlinear, the linearized, and the truncated system shows the existence of instability depending on the nonlocality parameter.

DIVERSE METHODOLOGICAL ANALYSIS OF MOVEMENT PATTERNS BY PURPOSE AND AGE IN SOUTH KOREA DURING COVID-19

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This study investigates the significant changes in movement patterns in South Korea during the COVID-19 pandemic using two distinct methodological approaches: intervention analysis and Autoencoder, a deep learning technique. Each method provides a unique perspective on the data, categorized by different purposes (office, residential, non-office activities) and age groups.

Intervention analysis is utilized to examine the immediate and direct effects of the pandemic and social distancing policies on movement patterns. This statistical approach helps quantify the impact of COVID-19 on societal mobility. Another methd, the Autoencoder model, is employed to uncover subtle, less apparent changes in these patterns. The contrasting insights from these methods offer a comprehensive understanding of the pandemic's impact on mobility and provide valuable guidance for future policy-making in response to global health crises.

SIMULATING VACCINE STRATEGIES THROUGH THE INTEGRATION OF A GENERATIVE MODEL THAT INCORPORATES A MATHEMATICAL MODEL OF VACCINE ANTIBODY DYNAM

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We experienced the COVID-19 pandemic and confirmed that vaccines are essential for pandemic control. However, reflecting on this experience, there were opportunities to optimize vaccination strategies, including the sequencing and intervals of vaccinations. To address these issues, it is crucial to comprehend the diversity of individual vaccine-induced immunity and formulate efficient vaccination strategies grounded in scientific evidence. In this study, we utilized time-series data on antibody titers and comprehensive health information (demographics, medical history, side effects, medication records, lifestyle, etc.) collected from the Fukushima vaccine cohort, one of the world's largest (2,500 participants) and longest-running (3 years) cohorts. We developed a generative model that integrates a mathematical representation of vaccine antibody dynamics. Essentially, we established a virtual vaccine cohort capable of suggesting vaccination strategies for combatting future pandemics.

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SIS-TYPE COVID-19 SPREAD WITH COLLECTIVE EFFECTS

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Many models developed for COVID-19 spread are complex (SIR+) and few include effects of collective behavior. As the pandemic progressed individual recurrent infection was observed and simpler SI/SIS type models were introduced. However, these do not include mechanisms to model collective behavior. Here, a generalization of the SIS model that accounts for collective behavior is introduced and shown to have four equilibria. The two standard SIS model equilibria, a third that is always unstable, and a fourth where collective behavior and infection prevalence interact to produce either node-like or oscillatory dynamics. When this general model is parameterized using estimates of the transmission and recovery rates for COVID-19 we find that regions of oscillatory dynamics exist and that the collective behavior parameter regulates their extent. We also find that the system exhibits hysteresis when the collective behavior parameter varies over time. Finally, we extend the model further by making the collective behavior component more general and show how this affects the dynamical properties of the model. This model and its generalization provides a minimal framework for explaining and exploring oscillatory phenomena such as recurring waves of infection and hysteresis effects observed in COVID-19 and other SIS-type epidemics in terms of collective behavior.

PATTERN FORMATION IN MECHANOCHEMICAL MODELS

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It is well known that chemical as well as mechanical cues play an important role in morphogenesis. To study this interaction, we derive and analyse a so-called mechanochemical model, which describes a biological surface (e.g. a cell membrane or a tissue surface) that is evolving over time, driven by the morphogen concentration and the surface curvature [1]. We study the one-dimensional version of this model, where the surface is described as a curve. There is a chemical diffusing on the curve that is locally inducing its curvature. The curve is constrained by its fixed global length, inducing an inhibiting effect.

Numerical simulations show many interesting patterns developing over time. We use an analytic tool called Geometric Singular Perturbation Theory to understand these numerical simulations [2]. We show the existence of particular periodic patterns, highlighting the importance of pattern selection by the geometric constraints of the curve.

The mechanochemical model has an interesting link with experimental work on Septin, a membrane binding, curvature-inducing molecule. Incubated in particular conditions, Septin can induce the formation of golf ball patterns on lipid vesicles [3]. Septin plays an important role in many processes, like cell division and cell motility. Understanding the pattern formation process visible in vitro can help unravel Septin's biological mechanism.

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VARIABLE SELECTION FOR NONLINEAR DIMENSIONALITY REDUCTION OF BIOLOGICAL DATASETS THROUGH BOOTSTRAPPING OF CORRELATION NETWORKS

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Identifying the most relevant variables or features in massive datasets for dimensionality reduction can lead to improved and more informative display, faster computation times, and more explainable models of complex systems. Despite significant advances and available algorithms, this task generally remains challenging, especially in unsupervised settings. In this work, we propose a method that constructs correlation networks using all intervening variables and then selects the most informative ones based on network bootstrapping. The method can be applied in both supervised and unsupervised scenarios. We demonstrate its functionality by applying Uniform Manifold Approximation and Projection for dimensionality reduction to several highdimensional biological datasets, derived from 4D live imaging recordings of hundreds of morpho-kinetic variables, describing the dynamics of thousands of individual leukocytes at sites of prominent inflammation. We compare our method with other standard ones in the field, such as Principal Component Analysis and Elastic Net, showing that it outperforms them. The proposed method can be employed in a wide range of applications, encompassing data analysis and machine learning.

MULTISCALE INFANT GUT MODEL PREDICTS THAT MILK OLIGOSACCHARIDES DECREASE MUCIN CONSUMPTION BY FEEDING BACTERIA THAT DON'T SHARE PUBLIC GOODS

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Intestinal mucin acts as a barrier protecting the infant gut wall against diseases such as colitis and rotavirus. We use a multiscale computational model of the ecology and metabolism of the infant gut microbiota to predict the effects of human milk oligosaccharides (HMO) on infant gut mucin. In vitro, the gut microbiota of breastfed infants consumes less mucin than the microbiota of non-breastfed infants, but the mechanisms are incompletely understood. Because many infant formulas do not contain HMO, we hypothesize that HMO protect the mucin layer by favouring non-mucin consuming bacteria in the microbiota.

We analyse this system using a computational modelling approach combining metabolic models with dynamic models of the spatial distribution of bacterial populations, and extracellular concentrations of lactose, mucin, and bacterial metabolites. Metabolism is calculated using flux balance analysis with additional metabolic constraints and a set of equations for modelling the extracellular production of public goods.

We compare the mucin consumer Bifidobacterium bifidum and the non-mucin consumer Bifidobacterium longum. B. longum digests HMO intracellularly, making it grow less efficiently on HMO in monocultures than B. bifidum that digests HMO extracellularly. The model suggests that in presence of the HMO 2'-fucosyllactose (2'-FL), extracellular digestion of 2'-FL by B. bifidum makes this species vulnerable to competitors, including Bacteroides vulgatus, because the digestion products become public goods and are consumed by B. vulgatus instead of by B. bifidum itself. The model predicts that B. longum can then become dominant, because it does not produce public goods. We conclude that the theory of public goods in microbial ecology may be key to understanding the effects of HMO on the mucin-consuming potential of the developing infant gut microbiota.

AGENT-BASED AND CONTINUUM MODELS FOR SPATIAL DYNAMICS OF INFECTION BY ONCOLYTIC VIRUSES AND ITS INTERACTION WITH THE IMMUNE SYSTEM

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The spatial dynamics between cancer cells and oncolytic viruses is still poorly understood; the interactions with the immune system constitute an additional challenge. We first neglect immune response and present a stochastic agent-based model describing infected and uninfected cells for solid tumours, which interact with viruses. Two kinds of movement, namely undirected random and pressure-driven movements, are considered: the continuum limit of the models is derived and a systematic comparison between the systems of partial differential equations and the individual-based model, in one and two dimensions, is carried out.

We observe a wide parameter range in which the infection of the agents remains confined to the center of the tumour, even though the continuum model shows traveling waves of infection. This suggests that the presence of spatial constraints in tumours' microenvironments limiting free expansion has a very significant impact on virotherapy. Some of these situations allow us to qualitatively reproduce patterns observed in experiments in vitro, suggesting that stochastic events may play a central role in the use of oncolytic virotherapy.

We then extend our previous work to include interactions with the immune system. In some cases we observe oscillations of cell number both in the discrete model and in the continuum counterpart, in line with the behaviour of the corresponding nonspatial model, which presents Hopf bifurcations. Furthermore, the discrete model may show asymmetric patterns absent in the continuum model. Our results highlight that an excessive immune response before the infection is well-established appears to decrease the efficacy of the therapy and thus some care is needed when oncolytic virotherapy is combined with immunotherapy.

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QUALITATIVE ANALYSIS IN A DISCRETE-TIME MODEL OF COMPETING PREY WITH A SHARED PREDATOR

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This paper concentrates on the study of a discrete time model of competing prey with a shared predator. The condition for existence and local stability of positive fixed point are derived. By using an iteration scheme and the comparison principle of difference equations, it is possible to obtain the sufficient condition for global stability of the positive fixed point. The sufficient criterion for Neimark-Sacker bifurcation and flip bifurcation are established. The system admits chaotic dynamics for a certain choice of the system parameters which is controlled by applying hybrid control method. The obtained results are verified through numerical simulations.

DECODING YEAST METABOLISM UNDER BATCH FERMENTATION WITH A MULTI-PHASE DYNAMIC GENOME-SCALE MODEL

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Batch fermentation is widely used in industrial and food biotechnology to produce various products, including antibiotics, enzymes, and biofuels. The process is led by microorganisms which follow multi-phase growth dynamics. Each phase plays a specific role in producing the desired product characteristics. Their durations depend on the selected microorganism species or strain, the fermentation medium, and the environmental conditions (e.g. temperature, pH).

Recently, a discontinuous multi-phase multi-objective dynamic Flux Balance Analysis (dFBA) approach was suggested to explain primary and secondary metabolism in batch fermentation at the genome scale. However, the model lacked a mechanistic connection between the phases and the implementation required modifying the constraints and objective function in every phase, thus complicating its use by non-experts.

Here, we propose a continuous multi-phase modelling approach. We combine an extracellular kinetic model that automatically handles different phases using an empirical description of metabolic regulation with a genome-scale model to predict intracellular fluxes. In this approach, we impose the extracellular dynamics as continuous constraints in the FBA formulation and define the cellular objective as a time-varying compromise between ATP and protein production.

We have applied the model to successfully explain the metabolism of three yeast species in batch fermentation conditions. We calibrated the model using time-series data for more than 40 variables, including biomass dynamics, nitrogen and carbon sources, and different products (alcohols, acids, esters). Results compare well with the discontinuous model, and flux distributions are biologically meaningful.

This new continuous dynamic genome-scale model can be easily adapted to explore the metabolic potential of alternative yeast species in industrial and food biotechnology.

JUMP-SWITCH-FLOW: HYBRID DETERMINISTIC-STOCHASTIC TRAJECTORIES OF COMPARTMENTAL SYSTEMS

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Many dynamical systems exhibit multiscale behaviour. A classic example of this is the atto-fox problem in the Lotka-Volterra predator-prey model where oscillations lead to populations becoming unfeasibly small. Similar issues arise in epidemiology, immunology, and molecular biology, where small populations may go extinct due to stochastic effects. One resolution is to represent the process as a continuous time Markov chain (CTMC) which accounts for the discrete nature of small populations. Unfortunately, for large populations, simulating this process is computationally intractable. We have developed a way to approximate the CTMC which preserves the discrete stochastic behaviour of small population sizes, and continuous deterministic behaviour of large populations. Depending on the state of the system, the process switches between stochastically (jumping) and deterministically (flowing). We call this approach 'Jump-Switch-Flow' (JSF). In addition to incorporating small population stochastic effects, our approach also has a natural notion of compartment extinction, providing a solution to Atto-type problems.

Here, I will present JSF (an open-source package implementing this approximation) and demonstrate, through a simulation study of an epidemiological SIRS model with demography, that it reproduces much of the behaviour of current gold standard exact simulation techniques, while being substantially faster. I will also show, using synthetic data as a toy example, how JSF lets us discuss elimination scenarios under intervention. Finally, using clinical data of SARS-CoV-2 infections, I will demonstrate how JSF enables the analysis of within-host processes, while accounting for viral clearance.

TWO-VECTOR TRANSMISSION DYNAMICS OF THE DENGUE VIRUS

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Compartmental models have been used in the past for studying the transmission dynamics of the dengue virus. The sole transmission vector is often assumed to be the Aedes aegypti mosquito found predominantly in tropical climates. In recent times, it has been proven that the dengue virus can also be transmitted (albeit to a lesser extent) by the Aedes albopictus mosquito species which is endemic in many tropical and sub-tropical regions. With the advent of climate change, it is expected that the Northern Hemisphere will have extended Aedes aegypti and Aedes albopictus distributions, while the Southern Hemisphere will have the opposite outcomes. Europe is expected to become more suitable for both species and their related vector-borne diseases.

We propose a mathematical model for the dengue virus in regions where Aedes aegypti and Aedes albopictus mosquitoes would coexist. For simplicity, the SIR (Susceptible-Infected-Recovered) model is adopted for the human population with SI (Susceptible-Infected) compartments assumed for each vector species. We identify a disease-free equilibrium and two endemic equilibria. The Next Generation Method is utilized to find the basic reproduction number and investigate the local asymptotic stability of the equilibrium states. Numerical simulations of the model are generated for reasonable estimates of the parameter values. By comparing our results with a degenerate version of the model with only one vector present, we find the peak of viral outbreak to be significantly enhanced with the second mosquito vector present.

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INCORPORATING HETEROGENEITY IN FARMER DISEASE CONTROL BEHAVIOUR INTO A LIVESTOCK DISEASE TRANSMISSION MODEL

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Disease management behaviours of farmers are crucial to disease control in their livestock, whilst also contributing to the success of wide-scale disease control. Heterogeneity in farmer behaviour towards disease management therefore warrants consideration when establishing veterinary health policies. However, analytical approaches that can contribute insights to livestock disease control plans, such as mathematical modelling, traditionally omit variation in farmer disease management behaviours.

We present a methodological pipeline developed to generate novel quantitative data on farmer beliefs with respect to disease management, process the data into a form amenable for use in mathematical models of livestock disease transmission and then refine said mathematical models according to the findings of the data. We discuss our application of this methodology for a fast, spatially spreading disease outbreak scenario amongst cattle herds in Great Britain, for which we elicited when farmers would use an available vaccine. We then used the attained behavioural groups within a spatial livestock disease model to make epidemiological and health economic assessments.

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A VIRTUAL LAB FOR PARKINSON'S DISEASE: MODELING ALPHA-SYNUCLEIN AGGREGATION DYNAMICS

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The neuronal protein alpha-synuclein (aSyn) holds a crucial role in the intricate molecular landscape of Parkinson's disease. Indeed, recent advances in aSyn-based biomarkers have led to the definition of a new biological framework for the disease. Aggregates such as oligomers and fibrils have also been suggested as key pathogenic triggers and potential therapeutic targets. However, many unclear aspects and mechanisms linked to aggregation hamper the quest for effective disease-modifying therapies. To address these knowledge gaps, experimental research calls for a quantitative systems pharmacology approach [1].

We propose a mathematical model of the complex chemical reaction network underlying aSyn aggregation. The ordinary differential equation system captures a nucleation-conversion-polymerization process with toxic oligomers at the core and self-amplifying loops, including all the microscopic events explicitly related to aSyn in the literature. Model calibration and validation rely on experimental data from in vitro aggregation assays [2, 3]. To assess parameter reliability, we also performed local-at-a-point and structural identifiability testing and uncertainty quantification.

The model can capture multiple scenarios of aSyn accumulation mimicking in vivo settings in agreement with the underlying biological processes. In addition, our model enables a broad spectrum of in silico experiments exploring the impact of risk factors such as aging and gene mutations through specific proxies in the model, e.g., lipid-to-protein ratio, pH level, and monomer concentration. Finally, model predictions and results of local sensitivity analysis are associated with the effects of compounds currently under investigation, suggesting candidate target mechanisms to counteract aggregation.

Overall, this work provides a robust mathematical framework for investigating disrupted aSyn homeostasis and a virtual lab for testing anti-aSyn aggregation therapies.

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A MULTISCALE PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) PLATFORM TO SUPPORT THE DEVELOPMENT OF MRNA-ENCODED THERAPEUTICS

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In recent years, numerous antibody-based therapeutic agents have exhibited significant potential, especially for diseases like cancer. Despite their efficacy, many antibody drugs remain plagued by high costs, intricate production processes, and the persistent challenge of a short half-life. In contrast, the endogenous expression of therapeutic proteins via in vitro-transcribed (IVT) mRNA formulations has turned out to be a more adaptable and cost-efficient alternative. mRNA therapies harness the cellular machinery to instruct the production, within the patient's own cells, of therapeutic proteins with an extended half-life. Along with these new technologies comes the need for robust tools to explore the intricate dynamics of drug trafficking at the whole-body level and its efficacy. Mathematical modelling can be crucial to fully harness the potential of mRNA-encoded therapeutics, functioning as virtual laboratories for dose and schedule-finding applications. In this study, we present a multiscale mathematical model capable of mimicking both the recombinant and mRNA-encoded protein trafficking. Expanding upon the two-pore Physiologically Based Pharmacokinetic (PBPK) model introduced in [1], we added a layer describing the mRNA trafficking, uptake, translation, and clearance. The multiscale nature of our PBPK model facilitates a comprehensive understanding of target protein synthesis and tissue distribution mechanisms, thereby enhancing the accuracy of drug concentration predictions in specific organs, especially at the site of action. Our model is implemented in MATLAB Simbiology, and it has been successfully fitted and validated on proteins of variable size using literature times-series data [2,3]. Despite validation limited to preclinical animal models due to data availability constraints, our model exhibits excellent translational properties and holds the potential to serve as a valuable tool for in silico supporting the development of mRNA-encoded therapeutic.

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A MATHEMATICAL MODEL IN EVOLUTIONARY MEDICINE: COORDINATED INHERITANCE OF EXTRACHROMOSOMAL DNA TYPES

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Cancer cells evolve through complex mechanisms, including copy number alterations such as amplification of oncogenes, facilitating their escape from normal tissue regulation. Extrachromosomal DNA (ecDNA) plays a crucial role in this process by releasing oncogenes outside the normal chromosomal constraints, enabling accelerated evolution, significantly improving oncogenic transcription and promoting tumor expansion and treatment resistance. Furthermore, multiple ecDNA types coexist within cancer cells, facilitating intermolecular gene activation and somatic mutations that alter sequence diversity and function. ecDNA's sensitivity to epigenetic states and microenvironmental stressors further enhances its role in tumor progression and adaptation. Various models have already been developed to explain ecDNA origin and proliferation paths, highlighting its random inheritance during cell division and intercellular copy number heterogeneity, but very little has been investigated about co-occurrence of multiple ecDNAs and their mutual interactions. We then propose a mathematical model which describes a multiple-types evolutionary process, with a special focus on the mechanisms that drive ecDNA co-occurrence in populations, such as phenotypical and fitness alteration, and we investigate the effects that these have on copy number distribution and correlation, cell selection strength, evolutionary trends over time. Overall, our model provides a framework for understanding the formation and behaviour of ecDNA genomic structures and may have implications for the development of new strategies for detecting and treating cancer.

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LIBPSPM: A FEATURE-RICH NUMERICAL PACKAGE FOR SOLVING PHYSIOLOGICALLY STRUCTURED POPULATION MODELS

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For a vast majority of organisms, life-history processes depend on their physiological state, such as body size, as well as on their environment. Size-structured population models, or more generally, physiologically structured population models (PSPMs), have emerged as powerful tools for modelling the population dynamics of organisms, as they account for the dependencies of growth, mortality, and fecundity rates on an organism's physiological state and capture feedbacks between a population's structure and its environment, including all types of density regulation. However, despite their widespread appeal across biological disciplines, few numerical packages exist for solving PSPMs in an accessible and computationally efficient way. The main reason for this is that PSPMs typically involve solving partial differential equations (PDEs), and no single numerical method works universally best, or even at all, for all PDEs. Here, we present libpspm, a general-purpose numerical library for solving user-defined 1- and multi-dimensional PSPMs. libpspm provides eight different methods for solving the PDEs underlying PSPMs, including four semi-implicit solvers that can be used for solving stiff problems. Users can choose the desired method without changing the code specifying the PSPM. libpspm allows for predicting the dynamics of multiple physiologically structured or unstructured species, each of which can have its own distinct set of physiological states and demographic functions. By separating model definition from model solution, libpspm can make PSPM-based modelling accessible to non-specialists and thus promote the widespread adoption of PSPMs.

EVALUATING TARGETED VECTOR-CONTROL STRATEGIES FOR MALARIA ELIMINATION IN CAMBODIA'S FORESTED REGIONS: A STOCHASTIC MODELLING APPROACH

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Cambodia has achieved over 95% reduction in malaria cases from 2010 to 2021, with no malaria deaths since 2018. The disease is now concentrated in forested regions, affecting primarily forest dwellers and workers. Traditional vector-control tools are less effective in these areas. In response, new strategies like insecticide-treated clothing and volatile-pyrethroid spatial repellents (VPSRs) are being explored. These methods target mosquitoes that bite outdoors and during the day, potentially offering better protection in forest settings. Firstly, we parameterise hierarchical Bayesian models to data from entomological studies evaluating these interventions. bite frequency amongst individuals in the population and evaluate the impact of targeting interventions towards forest dwellers and workers, who are most exposed to infectious mosquito bites. This model incorporates factors such as vector behaviour, medical systems, and care-seeking behaviours to predict the effectiveness of these interventions. Analysis indicated that these new interventions could significantly aid Cambodia's goal of malaria elimination. Adherence to intervention usage significantly impacts the efficacy of these interventions. Therefore, VPSRs are likely more viable, being passive objects and low-maintenance. In some settings, the same reduction in clinical cases can be achieved with 20% of the product by targeting forest goers and dwellers and increasing adherence within these populations. This study suggests targeting interventions at forest goers and dwellers would be a cost-effective strategy to help achieve malaria elimination in Cambodia, and the wider Greater Mekong Subregion. Low adherence to the use of tools significantly reduces their efficacy, therefore community engagement is essential in ensuring tools distributed are tools local communities want to use and know how to use correctly.

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A MODEL OF SELF-ORGANIZING AXON PATHFINDING IN THE FLY VISUAL SYSTEM

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During neural superposition wiring in Drosophila, several thousand axons grow towards their corresponding postsynaptic targets with almost no errors. Remarkably, this process works without target-dependent guidance and even in the absence of all target neurons (Agi, Reifenstein et al., 2024). To elucidate the underlying mechanism, we perform intravital imaging of growth cone dynamics in vivo and use the obtained data to inform a computational model of axon growth. The core of the model is stochastic filopodial exploration of a growth cone's surrounding, which is - in turn - shaped by the growth cones themselves, bearing hallmarks of self-organization. We discuss the self-organization aspect of the model, show that the model reproduces the biological reality for a broad range of conditions, and demonstrate that the self-organization aspect increases the model's robustness towards perturbations, suggesting self-organization as a more general feature of developmental wiring processes in the brain.

ASSESSING THE TRANSMISSION POTENTIAL OF MPOX IN EAST ASIA DURING 2022-2023: A FOCUS ON TAIWAN, CHINA, JAPAN, AND SOUTH KOREA

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This study aims to estimate the transmission potential of mpox in East Asia, focusing on the hardest hit nations: Taiwan, China, Japan, and South Korea. To fit the case incidence during the initial 30 epidemic days, we utilized six phenomenological dynamic growth models. The best-fit model was selected to calculate the reproduction number (Rt). Additionally, we used the latest case data and a Bayesian framework to compute the instantaneous effective Rt by applying the Cori et al. method. During the early phase, China demonstrated the highest estimated Rt of 2.89 (95% CI: 1.44-3.33); followed by South Korea, 2.18 (95% CI: 0.96-3.57); Japan, 1.73 (95% CI: 0.66-3.94); and Taiwan, 1.36 (95% CI: 0.71-3.30). However, by June 30, 2023, estimated Rt dropped below 1.00 in all countries: China at 0.05 (95% credible interval [CrI]: 0.02-0.10), Japan at 0.32 (95% CrI: 0.15-0.59), South Korea at 0.23 (95% CrI: 0.11-0.42), and Taiwan at 0.41 (95% CrI: 0.31-0.53), indicating the potential decline of the outbreak. Our analysis shows effective containment by each country. It is crucial to sustain effective management to ensure the ultimate eradication of the outbreak.

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DEPLOYMENT OF GENETIC VARIABILITY IN TREESCAPES: INSIGHTS FROM A BIOECONOMIC MODEL

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The UK government aims for net zero greenhouse gas emissions by 2050, with carbon capture via tree planting at the centre of their strategy. Trees have substantial adaptive capacity, harnessing high levels of genetic variation and plasticity to handle environmental pressures, but with a changing climate and emerging pests and diseases, they may not adapt quickly enough to maintain their provision of key ecosystem services. Tools are therefore needed to help managers and policymakers maintain forest resilience. Tree pest and disease spread models have often focused on single-host, single-pest combinations, overlooking intraspecific variation in host susceptibility. Further, the role of tree intraspecific genetic variability remains unexplored through a forest economics lens. Here, we develop a bioeconomic model that explores the long-term consequences of various distributions of genetic variability. Specifically, we extend an optimal rotation model to include within-stand intraspecific variation in growth rates and disease response. We perform a net present value analysis of timber returns to assess planting and management strategies, using numerical optimisation of an integral over time. Epidemiological partial differential equations with continuous variation in susceptibility model the feedback loops between genetic variability and disease dynamics. Changes in the composition of the planted forest result in trade-offs between the costs of deployment of novel traits and potential gains from protection against threat species and climate change. There is an incentive to plant high levels of genetic variability when the suppressive effects on pest or disease dynamics outweigh the economic losses from harvesting trees at mixed or lower maturity levels. Even if there is a cost of resistance, planting slower-growing and more resistant trees can be optimal if rotation periods are long and disease outbreaks are likely.

A MODEL FOR SIMULATING PLAQUES FORMATION IN ALZHEIMER'S DISEASE

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Amyloid-beta peptides accumulate in the brain forming plaques that are related to the progression of Alzheimer's disease. Reduced exchange of nutrients across the blood-brain barrier level, as well as impaired brain clearance are a consequence of this toxic precess. We present a compartment model to help determinining therapies to hinder disease progression. The effects of the latter are studied via 'in silico' simulations. Sensitivity analysis is carried out to assess the most important parameters on which these therapeutic measures should concentrate.

EXPERIMENTAL DATA INFORMS MOLECULAR CLUSTER PREDICTION IN MITOCHONDRIA

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Mitochondria are widely known as the powerhouse of the cell and, thus, a very important membrane bounded organelle. Besides its key function in the energy metabolism, it is also involved in a variety of other cell functions and pathways, like intracellular signalling, cell growth and cell death. A mitochondrion is shielded from the rest of the cell by a double membrane with the inner membrane weaving through the whole organelle's body forming compartments. The membranes, the intermembrane space and the so-called matrix, the space surrounded by the inner membrane, contain an abundance of proteins, which form complexes that mediate the different processes in mitochondria. However, while functions and pathways (in health and disease) are still found, corresponding complexes need to be discovered. In order to probe protein complex formation in Mitochondria, we employ molecular dynamics simulations, in which the potentials governing the interactions are directly informed from data obtained via cross link mass spectrometer. The simulations include representations of proteins bound to the membranes as well as freely moving proteins from the inter membrane and matrix domain approximating their natural environment. Through a number of simulations, different protein complexes form. We will find, that the known complexes are recovered, while other new complexes make an appearance. Especially the new complexes might then be experimentally identified and another functions of Mitochondria might be explained.

MODELLING BACTERIAL CHEMOTAXIS IN BIOFILMS

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Biofilms are structured communities of microorganisms that adhere to surfaces and are embedded in a self-produced matrix of extracellular polymeric substances (EPS). These ecosystems constantly evolve in response to environmental fluctuations, and exhibit intricate dynamics governed by interconnected mechanisms. In recent decades, bacterial chemotaxis has been identified as a pivotal factor contributing to the spatial organization and composition of biofilm communities by regulating cell motility. Indeed, bacteria respond to external changes by moving directionally towards attractants or away from repellents. This process is an important responsive mechanism that allows bacteria to adapt to new environmental conditions and optimize their positioning within the biofilm. Since biofilms are studied in extremely varied fields, including medicine, environmental science, and industry, understanding chemotaxis in biofilms is essential for revealing the complex dynamics of these microbial communities.

In this context, a mathematical model is proposed to describe biofilm growth dynamics, including the spatial distribution of microbial species, substrate concentrations, metabolic cooperation and/or competition between species, and, in particular, the motility of planktonic cells within the biofilm matrix. Such model is formulated as a hyperbolic – parabolic free boundary value problem. It considers two state variables representing the planktonic and sessile phenotypes and reproduces the transition from one state to the other. Additionally, two different planktonic cells motion behaviours are considered: random motility governed by the diffusion process, and directional motility driven by chemotactic responses to chemical gradients. The proposed model is applied to a case of biological and ecological interest to investigate biofilm evolution during biologically relevant conditions and explore the influence of the chemotaxis process on biofilm dynamics and ecology.

SOCIAL VS. INDIVIDUAL AGE-DEPENDENT COSTS OF IMPERFECT VACCINATION

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In diseases with long-term immunity, vaccination is known to increase the average age at infection as a result of the decrease in the pathogen circulation. This implies that a vaccination campaign can have negative effects when a disease is more costly (financial or health-related costs) for higher ages. This work considers an age-structured population transmission model with imperfect vaccination. Our aim is to compare the social and individual costs of vaccination, assuming that disease costs are age-dependent. A model coupling pathogen deterministic dynamics for a population consisting of juveniles and adults, both assumed to be rational agents, is introduced. The parameter region for which vaccination has a positive social impact is fully characterized and the Nash equilibrium of the vaccination game is obtained. Finally, collective strategies designed to promote voluntary vaccination, without compromising social welfare, are discussed.

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MODELLING LASER-INDUCED THERMAL ABLATION: INCORPORATING TISSUE WATER CONCENTRATION AND ITS VAPORIZATION EFFECTS FOR LIVER CANCER TREATMENT

Federico Herrero Hervás (Universidad Complutense de Madrid)

Thermal ablative procedures enable tissue destruction through prolonged exposure to either very high or very low temperatures, inducing hyperthermia or hypothermia, respectively. This approach proves particularly effective in treating certain tumors, such as liver cancers, which are often inoperable. In this work, we introduce a novel model [ref. 1] for laser-induced thermal ablation, describing the evolution of tissue temperature and its water concentration during exposure to a heat source supplied by a laser applicator.

The main novelty of the model, with respect to previous works in the field, lies in considering tissue water concentration as a new variable, instead of as a known function experimentally fitted. Furthermore, the model incorporates a modulation effect in the temperature evolution, accounting for the vaporization of tissue water. Temperature growth is flattened before reaching 100ºC, as the thermal energy provided by the laser applicator does not contribute to a temperature increase and is instead used for the phase change in the irradiated areas.

The model hence consists of two coupled equations: a parabolic partial differential equation for the temperature T and an ordinary differential equation for the water concentration w. The equation for T is a modified version of Pennes' bioheat equation, accounting for temperature diffusion, blood perfusion, the laser applicator's heat source, and the vaporization effects near 100ºC. The equation for w respectively represents the loss of tissue water that occurs during vaporization through a known function.

The model equations are solved in a cylindrical domain around the laser applicator with realistic parameter values obtained from the literature [ref. 2]. Comparison with existing experimental data for porcine liver tissue reveals a very good fit, with simulated temperatures exhibiting minor discrepancies, mostly below 1ºC, compared to the experimental results.

[1] Herrero-Hervás, F., Farina, A. (2023) A new coupled model for laser-induced thermal ablation accounting for tissue water vaporization. arXiv. https://doi.org/10.48550/arXiv.2312.13457

OPTIMIZING EPIDEMIC RESTRICTIONS THROUGH PIECEWISE TIME-VARYING SIRD MODELS: A CASE STUDY OF THE COVID-19 EMERGENCY IN ITALY

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The ongoing global COVID-19 pandemic has had profound effects on both economic and healthcare systems worldwide, prompting governments to grapple with the complex task of devising containment strategies that aim at balancing the control of virus transmission and the limitation of social and work activities. In the paper [1] we introduce a framework for the real-time optimization of epidemic restrictions, employing a time-varying SIRD model. Despite their simplicity, these models effectively capture crucial epidemic spread features, with their inherent parameter variability enabling accurate adaptation to real-world data. We formulate an optimization problem that carefully weighs health and economic costs, solving it parametrically through a receding-horizon approach. This results in an optimal sequence of social contact restrictions, assumed to be implemented through governmental containment measures. Numerical simulations utilizing real data from the Italian COVID-19 emergency underscore the potential efficacy of our proposed approach, offering valuable insights for decision-makers during both current and future pandemics.

[1] Borri, Alessandro et al. (2023). Optimizing restrictions in epidemics via piecewise time-varying SIRD models: Application to the COVID-19 Italian emergency. European Journal of Control, 75(1), 100902. https://doi.org/10.1016/j.ejcon.2023.100902

DYNAMICS AND VACCINATION CONTROL OF THE TRANSMISSION OF GONORRHOEA IN MSM, FEMALES AND NON-MSM MALES

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Gonorrhoea is a sexually transmitted infection caused by the bacterium Neisseria gonorrhoeae. The bacteria can infect the genital tract, rectum, and throat; if left untreated, it can lead to serious health complications. Gonorrhoea is a significant public health concern due to its increasing incidence and the emergence of drug-resistant strains. Men who have sex with men (MSM) are considered to be at an increased risk for gonorrhoea and form a potential core risk group. Studies have been devoted to investigating the transmission of gonorrhoea within MSM and the potential vaccination strategies. Evidence from New Zealand suggests that the MenB vaccine is also partially efficacious against gonorrhoea, though a specific vaccine is in development. Recent incidence data shows that the spread of gonorrhoea in females and non-MSM males has also been growing.

We developed a deterministic transmission model, incorporating asymptomatic and symptomatic infection and heterogeneous sexual behaviour in MSM, females and non-MSM males. We used Markov chain Monte Carlo methods to calibrate the model with gonorrhoea incidence data in England in 2013–2019; then, we examined an extensive range of scenarios.

We conclude that the development and implementation of a vaccine (even partially-protective) against gonorrhoea, delivered through an effective targeting strategy, could indeed have a significant impact on reducing the incidence of the infection.

DESIGNING VACCINATION STRATEGIES FOR EPIDEMIC MODELS USING MULTIPLE OPTIMAL CONTROLS

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The choice of the objective functional in optimization problems coming from biomedical and epidemiological applications plays a key role in optimal control outcomes. In this study, we investigate the role of the objective functional on the structure of the optimal control solution for an epidemic model for sexually transmitted infections that includes a core group with higher sexual activity levels than the rest of the population. An optimal control problem is formulated to find a targeted vaccination program able to control the spread of the infection with minimum vaccine deployment. Both L1- and L2-objectives are considered as an attempt to explore the trade-offs between control dynamics and the functional form characterizing optimality. The results show that the optimal vaccination policies for both the L1- and the L2-formulation share one important qualitative property, that is, immunization of the core group should be prioritized by policymakers to achieve a fast reduction of the epidemic. However, quantitative aspects of this result can be significantly affected depending on the choice of the control weights between formulations. Overall, the results suggest that with appropriate weight constants, the optimal control outcomes are reasonably robust with respect to the L1- or L2-formulation. This is particularly true when the monetary cost of the control policy is substantially lower than the cost associated with the disease burden. Under these conditions, even if the L1-formulation is more realistic from a modeling perspective, the L2-formulation can be used as an approximation and yield qualitatively comparable outcomes

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APPROXIMATION OF REPRODUCTION NUMBERS OF AGE-STRUCTURED MODELS

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For age-structured models, reproduction numbers are typically defined as the spectral radius of operators acting on infinite dimensional spaces. As a result, their analytical computation is hardly achievable without restrictive assumptions on the model coefficients (e.g., separability of age-specific transmission rates), hence numerical approximations are needed. I will present a new general numerical method for approximating the reproduction numbers of a class of age-structured models with finite life span, based on pseudospectral collocation of the relevant operators. The approach allows complete flexibility in the choice of the "birth/infection" and "transition" processes, hence allowing to approximate different reproduction numbers, including the most common basic and type reproduction number. The flexibility of the approach will be illustrated with several examples from infectious disease modelling by considering different interpretations of the age variable (e.g., demographic age, infection age, disease age) and the transmission terms (e.g., horizontal and vertical transmission).

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ANALYSING THE ENTRAINMENT DYNAMICS OF MODELS OF THE CENTRAL CIRCADIAN CLOCK

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Understanding the response of the central circadian clock to a shifted external environment is crucial for studying phenomena such as jet lag. Compared to other modelling approaches for the central circadian clock (e.g. delay models or van der Pol oscillators), the mathematical analysis of phase oscillators is less complex. A prominent phase oscillator is the Hopf oscillator, which we propose in combination with an external force (zeitgeber) as a model for the central circadian clock. The common basis of all these models is a periodic orbit (homeomorphic to S1), which is, without external force, translational invariant, but stiff in a perpendicular direction. That is, we have a symmetry group acting on the essential state space of the models, and the external force interacts with this symmetry group on a slow time scale. We use this universal basis as a starting point to investigate the phase dynamics of the Hopf oscillator. The resulting dynamics are, on the one hand, compared with similar considerations for other established models, such as the Jewett-Forger-Kronauer and on the other hand, the model predictions are tested against real-world data.

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ANALYTICAL BAYESIAN FRAMEWORK FOR DIFFERENTIAL GENE EXPRESSION ANALYSIS ON RNA-SEQ DATA

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Rapid advancements in RNA-sequencing technology have revolutionised our ability to capture the complete RNA profile in tissue samples (bulk RNA-Seq) and isolated cells (single cell RNA-Seq) at chosen time points.

This wealth of data allows for comparative analyses of RNA levels within cells and tissues, shedding light on temporal changes, developmental processes, environmental responses, and treatment effects.

However, unravelling the dynamics of gene expression still presents a challenge, given the inherent variability of the data stemming from biological fluctuations, technological limitations and measurement errors.

To address this, we introduce a novel, fully analytical Bayesian framework tailored to the differential gene expression analysis of processed RNA-Seq data.

Our framework unifies and streamlines a complex analysis, typically involving parameter estimations and multiple statistical tests, into a concise mathematical equation (i.e. we provide a closed-form or analytical solution to the problem). This formula can be implemented in a single line of code, enabling rapid and transparent analyses.

In addition to presenting our framework, we delve into the broader landscape of differential gene expression analysis, aiming not only to offer a new tool but also to provide insights into the underlying reasons for divergent results across existing methods.

We conducted a comprehensive comparison of our framework with leading differential gene expression tools, finding substantial overlaps in the results.

However, it is also interesting to look at where different methods diverge in the results. We leverage both simulated and real data and show how seemingly variable data can masquerade as differential expression while substantial changes remain undetected.

In light of these advances, we come back, over and over again, to the fundamental question: What precisely constitutes a differentially expressed gene?

PATTERN FORMATION IN STOCHASTIC REACTION-DIFFUSION SYSTEMS

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In recent work, we derived a complete classification of the simplest two-species mass-action reaction schemes which exhibit Turing instability. Each of these therefore has the potential to support stable patterned states.

A typical weakly nonlinear scaling reveals that, under suitable choices of reaction stoichiometry and for most classes of minimal scheme exhibiting spatially in-phase ("true activator-inhibitor") Turing instability, stable patterns can indeed bifurcate supercritically from the spatially uniform state. Intriguingly, some classes of minimal scheme require different weakly nonlinear scalings since coefficients in the usual normal form vanish unexpectedly.

In the case of a subcritical bifurcation, we conjecture that the unstable branch of patterned solutions will switch back through a saddle node bifurcation to admit stable patterned states below the Turing instability threshold, and thus allow bistability between the zero state and finite-amplitude patterned states. If this bistability is sufficiently robust to finite-size effects, then this implies a distinctive mechanism for pattern formation in stochastic systems: via stochastic switching between stable patterned and non-patterned states.

BIOECONOMIC MODELLING FOR SUSTAINABLE BIOLOGICAL CONTROL AGAINST A CABBAGE PEST

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Other authors: A. Kambeu Youmbi, S. Touzeau, B. Tsanou

Diamondback moth causes significant production loss on cabbage, one of the most important food crops around the world. Several techniques have been developed to limit the damages caused by this pest, such as parasitoid-based biological control. In this work, we considered a self-financing smallholder farm, whose sustainability relies on farm earnings covering operating costs and generating savings. We built a nonlinear bioeconomic model representing the dynamics of the cabbage biomass, the diamondback moth larvae population, the parasitoid population and the current financial account of the farm. The growth of parasitoids on larvae is modeled using the Beddington-DeAngelis type functional response characterized by mutual interference between parasitoids and by pest resistance to predation. We first studied the establishment of parasitoids without further intervention. We showed that pest reduction could be achieved by long-living parasitoids, though a Hopf bifurcation was observed, leading to oscillating behaviors. We then considered inundative biological control, where parasitoids are released continuously in the farm and proportionally to the funds available. We showed that too high a level of interference between parasitoids could prevent control. Otherwise, if the investment rate in biological control is high enough, the cabbage plantation could be protected. In addition, we computed the investment rate that maximizes the smallholder farmer's savings. Hence, this study provides both qualitative and quantitative foundations for the implementation of parasitoid-based biological control techniques under budget constraint.

MODELING OF THE OXYGEN AND CARBON DIOXIDE TRANSPORT THROUGH THE LUNG TO THE BLOOD.

Frédérique Noël (LJLL, Sorbonne Université, CNRS)
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The lung is a complex system that serves as an exchange interface between ambient air and blood. Its main function is to enrich the blood with oxygen and to deplete the blood with carbon dioxide through its tree-like structure. Once in the blood, hemoglobin is the primary carrier of oxygen. However, this affinity depends on the quantity of carbon dioxide in the blood. There is then, a competition between the two gases to link to hemoglobin in the blood. This is referred to as the Haldane and Bohr effects. The study of gas transport mechanisms and respiratory gases exchange with blood is a fundamental step to better understand how this complex system works. For this, a gas transport model composed of advection-diffusion-reaction PDEs for each species in one dimension has been developed [1]. This model takes into account the strong interaction between oxygen and carbon dioxide in the blood thanks to a coupled ODE system that represents the nonlinear coupling in the diffusion of the gases in the blood [2], [3]. This model ultimately allows to compute the quantity of oxygen and carbon dioxide exchanged with the blood over time as well as the oxygen and carbon dioxide blood partial pressure. The data predicted by the model are fully consistent with the physiological responses expected in the healthy case.

Subsequently, the model was extended to simulate some respiratory pathologies such as asthma and emphysema. A modeling was then carried out to take into account the different specificities of diseases and in particular, in order to take into account correctly their impact on the geometry of the lung (exchange surface, geometry of the bronchial tree).

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MODEL-BASED EXPERIMENTAL DESIGN TO IDENTIFY MICROBE INTERACTIONS

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Communities of microbes are known to adapt and improve their fitness by interacting with other species present in their environment. These interactions can either be positive or negative and can ultimately determine the success of a microbial community in nature or industry settings. Despite the importance of these interactions, identifying them can be challenging, particularly for the larger communities. One way to identify these interactions is to use metagenomics data, which can provide information on the relative abundance of certain species over time. These data can be analysed using a Generalised Lotka-Volterra model, which explicitly incorporates growth, carrying capacities and interaction coefficients. This work shows that this approach needs to be revised for communities with three or more species. Our mathematical analysis of the model reveals a lack of identifiability. Consequently, the model may recover experimental data well, but the estimated parameters may not accurately reflect the actual interactions. With an in silico example, we show how positive and negative interactions are confounded. To overcome this limitation, we formulated a model-based experimental design approach, and we illustrate its potential with an arbitrary three-species community in silico. The approach identifies the minimum number of experiments required to ensure identifiability; of course, the price to pay is the need for additional experiments or sampling conditions. However, the model-based design minimises the number of experiments needed.

OPTIMISING CANCER VACCINE EFFECTIVENESS VIA A DELAY DIFFERENTIAL EQUATION MODEL OF VARIABLE T CELL AVIDITY

Georgio Hawi (University of Sydney)
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Therapeutic vaccines have shown to be a promising avenue for the treatment of cancer through stimulating the immune system to attack and kill cancer cells expressing tumour-associated antigens. This is done by activating cytotoxic T lymphocytes (CTLs) which detect cancer cells via T cell receptor (TCR) recognition of peptide major histocompatibility complexes (pMHCs) on the surfaces of target cancer cells via major histocompatibility complex (MHC) class I. Avidity, the overall strength of a TCR-pMHC interaction, is an important factor to consider and corresponds to the likelihood of a CTL successfully killing a cancer cell. Low-avidity CTLs are not effective at killing cancer cells and may selectively inhibit high-avidity T cells, resulting in decreased antitumour activity. In practice, it is very difficult to preferentially select high avidity CTLs, which may justify the current lack of success of therapeutic peptide vaccines. We modify and improve upon a previously developed delay differential equation model of T cell avidity to analyse how vaccine-induced T cell avidity selection can be optimised to maximise the killing of cancer cells and to improve the clinical efficacy and durability of vaccine treatments for cancer. We perform sensitivity analysis to identify the most significant biological processes that could serve as targets for clinically successful therapeutic avenues. We finally optimise vaccine delivery by minimising a cost function that incorporates aspects including monetary costs, vaccine toxicity, cancer cell population and time taken for treatment success. In particular, we do not restrict ourselves to constant dosages and fixed time intervals as is common in the literature. Instead, we employ sophisticated model-independent optimisation methods to solve the more difficult problem of finding optimal therapeutic regimens with varying dosages and dosing frequencies – with the approach being easily applicable to many other biological models.

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TURING AND WAVE INSTABILITIES IN WATER-BIOMASS-TOXICITY MODELS FOR PATTERNED VEGETATION DYNAMICS

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In this talk we discuss the occurrence of Turing and wave instabilities in three-species vegetation models. In particular, we consider an extension of the classical Klausmeier model [1] in order to describe how the interaction among water, biomass and toxic compounds may lead to the emergence of stationary or travelling vegetation patterns. In this context, it is well established that the positive feedback regulation between water and plant biomass drives the growth of such structures in water-limited systems. However, this mechanism fails in those ecosystems in which water availability is not restricted. In these cases, the evolution of patterned dynamics is also affected by the presence of toxic compounds [2]. Indeed, it has been proved that the plant-soil negative feedback leads to an increase in soilborne pathogens, a change in soil microbial communities, and an accumulation of autotoxic compounds [3]. With this in mind, we aim at elucidating how the behavior of the emerging patterned structures may depend upon the combined effects of plant mortality, rainfall rate and auto-toxicity strength. To achieve this goal, linear stability analysis is firstly employed to characterize the loci of Turing and wave instabilities, so extracting information on the most relevant pattern features at onset. Then, to describe the time evolution of the amplitude close to the bifurcation thresholds, a multiple-scale weakly nonlinear analysis is employed for each considered instability. Finally, we also address results arising from numerical investigations to validate the theoretically-achieved predictions and, by simulating different ecological scenarios, to gain some additional insights into possible implications on ecosystems.

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EPIDEMICS ON EVOLVING SCALE-FREE GRAPHS ARE CRITICAL

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The evolution of epidemics and other contact processes depends on the interaction network between individuals. However, realistic networks are typically dynamic and change over time. We show that taking into account random shuffling of the network, a SIR-like epidemic becomes critical. Specifically, in any scale-free graph with infinite variance, periodic redrawing of degrees and the underling graph leads to a reproduction number that converges to one. In other words, the dynamics self-evolves into the critical threshold between exponential expansion and decay. Consequently, the entire population is infected and there is no herd-immunity. This dynamics occurs for all parameter values. Our results provide a possible explanation why some epidemics, in their final stages, do not decay exponentially as expected, but rather appear endemic over long timescales.

MATHEMATICAL MODELS OF HEPATITIS B INFECTION

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Nearly 300 million of people are chronically infected with hepatitis B virus (HBV) [1]. Currently no cure has been developed, leading to more than 800,000 HBV-related deaths annually [1]s. The focus of therapies is on eliminating the template for HBV replication, i.e. covalently closed circular DNA (cccDNA). However, HBV surface antigens (HBsAg) derive also from integrated DNA (iDNA) [2]. The presence of HBsAg activates the immune response, which leads to an inflammatory state and eventually to liver damage. Our collaborators at the Viral Hepatitis Center of John Hopkins University considered a cohort of 10 HBV-HIV co-infected participants on nucleos(t)ide analogue (NUC) therapy for a short or long time (from a few weeks to almost 12 years). Liver biopsies were obtained from each individual at 2 time points and single cell analysis was performed, measuring the genetic material inside each cell. First, we quantify the decay of the number of cells with viral genetic material, and its timescale, with the aim of understanding NUC therapy effects. Then, we build a stochastic model that accounts for hepatocytes spatial distribution to study the distribution of infected cells and how the viral genetic material accumulates inside each cell.

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MODELLING DRUG RELEASE FROM MICROCAPSULES WITH FUNCTIONALLY GRADED MATERIALS

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Drug releasing microcapsules and nanocontainers are largely used in pharmaceutical applications. Diffusion is by far the dominant mechanism in drug delivery, beside other physico-chemical factors, such as drug dissolution, drug binding, polymer swelling and degradation. We upgrade existing mechanistic models for drug release to non-homogenous substrates, and characterize the kinetics of the drug transferred from the vehicle into the external targeted medium.

The effect of non-homogeneity represents an important feature that can influence greatly the release characteristics. Functionally graded materials (FGMs) are a variety of composite materials in which properties vary smoothly and continuously from one region to another. This in contrast to the previous approach, such as layer-by-layer assembly, where there is an abrupt change in material properties. FGMs , i.e composite that have a progressive compositional gradient changing, are already currently and successfully used in a wide range of applications [1].

In this work, we present a space-dependent diffusion-reaction model for a spherical drug releasing system that extends the multi-layer configuration. Several possible space dependent forms for the diffusion and reaction shape-material functions are proposed. A analytical- solution expressed in terms of Fourier series is developed for this non-homogeneous mass transfer problem [2] . The drug concentration and release profiles show important differences with the uniform homogenous material case, providing guidance for design and development of microstructure of polymer platforms for drug delivery.

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EVOLUTION INTO CHAOS - IMPLICATIONS OF THE TRADE-OFF BETWEEN TRANSMISSIBILITY AND IMMUNE EVASION

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This study centers on the trade-off between immunity evasion and transmissibility. The inspiration behind this research arises from an examination of the behavior exhibited by Omicron variants, taking into account the fact that their heightened transmissibility may be attributed to their potent capacity to circumvent immune responses triggered by vaccinations and past infections. Our findings demonstrate the existence of a threshold for the transmission rate of the resident strain (βr), which dictates a shift in pathogen evolution towards immune evasion as the transmission rate increases. Moreover, we illustrate the long-term evolutionary patterns following the emergence of new strains with maximum invasion fitness. Under specific conditions, we established the global stability of the transmission rate for the new strain (βm) at the fixed point. The presentation of a bifurcation diagram and cobweb plots for βm unveils a spectrum of behaviors, ranging from chaotic dynamics to convergence towards the fixed point, offering a comprehensive insight into the intricate dynamics of the system.

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EXPLORING CANCER PROCESSES THROUGH THE BOOLEAN NETWORKS FRAMEWORK

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Modelling gene regulatory networks using Boolean networks is a firmly established approach. Boolean modelling constitutes a discrete approximation to the system of differential equations that would describe the transitions of the genetic network from one state to the next, a system that becomes intractable as the number of genes involved in the network is greater. In this framework, cell types are stable configurations of the dynamical system, that is, attractors. It has been argued that cancer cells can be viewed as abnormal attractors [1]; therefore, a way to study tumour evolution could be to find attractors of a Boolean network that recapitulates the process. The overwhelming number of possible networks requires filters to reduce it. A natural way to proceed is to identify some attractors from the available biological information and use them as a filter to reduce the number of networks compatible with the process. Here, we propose a practical method to perform the task. Furthermore, we will use the concept of canalisation, closely connected to biology, through nested canalising functions.

After applying filters for the selected attractors and obtaining all possible nested functions, those not coherent with the biological process are discarded. Then, the next step involves selecting the candidate nested functions describing the phenomenon. These selected functions will guide us towards new attractors, which will undergo a thorough analysis and subsequent discussion. In this manner, we can uncover novel potential stable states of the disease. Therefore, from the constructed Boolean network, it is possible to describe a theoretical evolution of the biological process that can be contrasted with experimental data.

The approach is illustrated with the Epithelial-Mesenchymal Transition, a relevant process in cancer, and bladder carcinoma data.

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A OPTIMAL AND MODEL PREDICTIVE OF GENE REGULATORY NETWORKS: DRIVING A POSITIVELY AUTOREGULATED GENE TO BI-MODAL BEHAVIOR

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In this study, we present a general framework for optimal and model predictive control (MPC) of gene regulatory networks through an external signal. This framework is founded on a general mathematical model introduced in a previous work, which approximates the chemical master equation of a general gene regulatory network, with this model we can obtain the gene expression distribution in a population. Building upon this model, we incorporate a control input on the transcription level of the network, this formulation enables us to control the probability distribution shape through this input, we establish first-order optimality conditions and a gradient formulation for different types of control inputs (continuous, piecewise constant), with this approach, we develop a nonlinear conjugate gradient optimization scheme to solve the optimal control problem that minimise the distance between the target probability distribution and solution of the mathematical model at predefined final time, as the goal is to shape the whole protein distribution on a population level rather than minimise a single point error, this framework is directly applicable with knowledge of network regulations and kinetic parameters. Furthermore, we develop a second algorithm to computationally assess the reachability of a target state using various control inputs and final times. Following this reachability test, we implement a MPC algorithm to not only achieve the target state but also stabilize the network around it or track several states. To illustrate the effectiveness of our framework, we apply it to two scenarios: first, a positively autoregulated gene that can be repressed with an external signal, demonstrating how MPC can induce bimodal behavior in this network that is initially unimodal. Secondly, we apply MPC to track multiple states in a generic case where a gene can be activated through an external signal, as in optogenetic control

THE IMPACT OF DEPRIVATION ON HETEROGENEOUS MIXING EPIDEMIC MODELS

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Deprivation has been one of the key factors underlying the differences in the way COVID-19 and similar infectious diseases affected different communities. Mathematical models are becoming more effective at including geographical and demographic elements in the spread of the disease, including differentiation in the rates of transmission, the effectiveness of self-isolation and lockdown, and the effectiveness of treatments like vaccinations and testing. The aim is to understand how people with different socioeconomic backgrounds are affected by the disease and how control can be applied in heterogeneous populations. We first analysed data to show that socioeconomic conditions significantly contribute to the increased prevalence of infectious diseases through multiple factors through the use of data analysis. Subsequently, we have conducted a detailed analysis of the behaviour of an infectious disease in heterogeneous connectivity-characterised metapopulation models. We consider the population split into subgroups, representing relatively deprived and wealthy parts of society. An SIR model is considered to capture risk values in which there are two groups with the same contact rates. The rate of infection increases more rapidly within high-transmission (deprived) groups when restricted mixing is considered since interactions with low-transmission (wealthy) groups limit the disease prevalence inside the high-transmission groups. Nevertheless, low-transmission groups see an increase in spread when they come into contact with high-transmission groups. When the mixing of two groups reaches its maximum degree, the connection between the reproduction number and the final epidemic size is evenly distributed for both groups.

POPULATION DYNAMICS OF TICK IN KOREA AND THE POTENTIAL IMPACT OF CLIMATE CHANGE AND CONTROL MEASURES

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Severe Fever with Thrombocytopenia Syndrome (SFTS) is a tick-borne disease that first emerged in China in the early 2010s and has since spread primarily in East Asia. There is currently no vaccine or antiviral drugs available to treat SFTS, and avoiding tick bites is the best way to prevent SFTS infection. In addition, ticks have a free and complex life cycle that depends on their species and the ecological environment of their habitat. Therefore, it is crucial to understand the ecology of ticks in Korea and implement control measures to manage the tick population. To address these issues, we developed a stage-dependent mathematical model to describe the ecology of ticks in Korea. The development rate of each stage of tick in the model takes into account a temperature-dependent parameter, as suggested by previous studies [1-3]. Using this model, we also examined the potential impact of climate change based on the Shared Socioeconomic Pathways (SSP) scenarios defined by the Intergovernmental Panel on Climate Change (IPCC). Furthermore, we simulated various scenarios, including mowing and spraying acaricide, which are commonly used to control tick populations, to predict the effectiveness of these control measures in managing the tick population.

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OPTIMIZING THE METHOD OF IMAGES FOR REGULARIZED STOKESLETS FOR SPHERE MOTIONS NEAR BOUNDARIES

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The general system of images for regularized Stokeslets (GSIRS) is used extensively to model Stokes flow phenomena such as microorganisms swimming near a boundary. To calibrate the GSIRS, we first utilize dynamically similar scaled macroscopic experiments to test the theories for forces and torques on spheres moving near a boundary. Then we discretize a unit sphere using the six-patch method and the spherical centroidal Voronoi tessellation (SCVT) method. Our data show that the SCVT method provides the most accurate results when the motional symmetry is broken by the presence of a boundary. Given a surface discretization for the sphere, the method of regularized Stokeslets is used to find optimal values for the regularization parameter in free space. We also present a regularization function with higher order accuracy to use with SCVT and the free-space-optimized regularization parameter. Our simulated force and torque values compare very well with experiments and theory for a wide range of boundary distances. However, we find that for a fixed discretization of the sphere, the simulations lose accuracy when the gap between the edge of the sphere and the wall is smaller than the average distance between grid points in the SCVT discretization method. Therefore, in addition to presenting an alternative method to calibrate the GSIRS to simulate sphere motion arbitrarily close to the boundary, we suggest an empirical rule for establishing the number of grid points necessary when discretizing a sphere. We conclude that using the GSIRS with a uniform point distribution such as the SCVT, a high-order regularization function, and a free-space-optimized regularization parameter provides an efficient and generally accurate method for simulating spheres moving near a boundary providing the edge of the sphere is kept outside of the average discretization length. See the accompanying talk by Bruce Rodenborn for our calibration of a motile bacterial model.

INFORMATION ACROSS SCALES: CAN INFORMATION ON PROTEIN STRUCTURE INFORM MODELS OF PROTEIN NETWORK DYNAMICS?

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Protein-protein interactions (PPIs) are ubiquitous in biology. Such interactions often involve bimolecular binding and are characterized by a dissociation constant, KD. Rather than considering PPIs in isolation, it can be useful to model the dynamics of PPI networks using ordinary differential equations (ODEs). However, as networks grow, so to do the number of KD's needed to parameterize the ODEs. Direct measurements often do not exist. Instead, these parameters must be inferred. The difficulty of this inference is compounded by the wide range of plausible KD's that must be considered. For example, the range of reported values from experimental databases spans more than 5 orders of magnitude[1]. We hypothesize that biophysical information for specific PPIs can reduce this uncertainty, and, ultimately, enhance parameter inference for ODE models of PPI networks. There are established regression models that predict a KD given a protein complex structure[2]. Further, if a complex structure does not exist, it may be predicted from an amino acid sequence using machine learning (ML) models[3]. We propose using regression and ML models in concert to predict a unique KD value for a given PPI. We test this approach on PPI's comprising ODE models of network dynamics and find that KD predictions refine the uncertain range derived from a database-only approach. Besides augmenting parameter estimation, our approach also offers insights into the generalizability of structure-based KD prediction.

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DYNAMICAL ANALYSIS OF AN HIV INFECTION MODEL INCLUDING QUIESCENT CELLS AND IMMUNE RESPONSE

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This paper presents a comprehensive analysis of an HIV infection model that incorporates quiescent cells and immune response dynamics within the host. The model, represented by a system of ordinary differential equations, captures the intricate interplay between the host's immune response and the viral infection. The study investigates the fundamental properties of the model, including equilibrium analysis, the computation of the basic reproduction number $\mathcal{R}_0$, stability analysis, bifurcation phenomena, numerical simulations, and sensitivity analysis. An infection equilibrium, which reflects the persistence of the infection, and a disease-free equilibrium, which represents the possibility of disease control, are both revealed by the analysis. By applying matrix-theoretical methods, stability analysis confirmed that the disease-free equilibrium is both locally and globally stable for $\mathcal{R}_0 < 1$. The research also reveals a transcritical forward-type bifurcation at $\mathcal{R}_0 = 1$, which denotes a critical threshold that affects the behavior of the system. The temporal dynamics of the model are investigated through numerical simulations, and sensitivity analysis determines the most important variables by examining the effects of parameter changes on the system's behavior.

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A NOVEL COMPARTMENTAL FRAMEWORK FOR MODELLING LYMPHATIC FILARIASIS DYNAMICS AND ELIMINATION STRATEGIES

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Lymphatic filariasis (LF) is a mosquito-borne neglected tropical disease caused by filarial worms. It is targeted for elimination by WHO within 2030. To guide and evaluate the elimination strategies, mathematical models can be helpful. In this paper, we propose and analyze a population level model of LF that can give estimates of disease burden, risk of resurgence in a non-endemic block and provide required number of mass drug administration (MDA) rounds to achieve the elimination threshold. Stability analysis of the model equilibria reveal that the disease-free equilibrium is globally asymptotically stable when basic reproduction number remains below unity. Global sensitivity analysis with respect to the equilibrium value of infectious humans is performed. Extensive scenario analysis and comparison with EPIFIL as well as LYMFASIM are performed to check robustness of the proposed model. We observe that the proposed model requires a similar number of MDA rounds to reach elimination as compared to EPIFIL. The proposed model can also give estimates of symptomatic disease burden for different scenarios. Additionally, the proposed model when extended to a two-patch system is capable of estimating resurgence risk of LF in a disease-free patch.

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A RETROSPECTIVE ANALYSIS ON THE ROBUSTNESS OF EXISTING COMPARTMENTAL MODELS FOR MODELLING FUTURE PANDEMICS

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Background & aims of study

For the duration of the Covid pandemic, the UK government consulted a number of mathematical models of transmission dynamics to help to guide policy response. Several of these epidemiological models use compartments to sort the population into and ODEs to describe the infection dynamics. However, these models rely on a number of modelling assumptions about the disease, which sacrifice accuracy for model tractability. These differences in turn impact the forecasts of the epidemic trajectory and may lead to incongruent recommendations to policy makers.

In this talk, we conduct a retrospective analysis of the performance of three models used for modelling the rapid progression of the Covid pandemic in the UK to test the robustness of the results and whether they can be used interchangeably to inform policy response: the "Cambridge-PHE" [1], the "Warwick Household model", and the "Roche model".

Methods & Results

For each model, we produce forecasts for cases, deaths and inferred instantaneous reproduction number trajectories both in the actual and in the unmitigated epidemic scenario, by fitting to the same early 2020 UK epidemic death dataset. We identified that each of the three considered models produced very different death and case trajectories in the counterpart scenario, i.e. when no non-pharmaceutical interventions are put in place, meaning that we cannot substitute the conclusions of on of these models for the other.

We also present the impact of pharmaceutical interventions as illustrated by all three models. Finally, we include a sensitivity analysis to assess robustness to parameter changes of the three models.

Implications

We hope this result to highlight the pitfalls of relying on single models to inform policy response in the context of future epidemics, as well as the need of a more in-depth study of the impact of modelling assumptions of the quality of model outputs.

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RESPIRATORY VIRUSES IN CARE HOMES: DEVELOPMENT OF TRANSMISSION MODELS

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Individuals living in long-term care (LTC) facilities were particularly heavily impacted by the COVID-19 pandemic and continue to experience significant burdens and challenges from common infectious diseases. It is imperative to comprehend the mechanisms by which infectious diseases transmit within, and between, such settings in order to minimise fatalities and other quality of life-reducing severe events.

I will describe strategies for implementing disease transmission models in close settings, particularly in care homes, resulting from joint work with UKHSA on enhanced data gathered from outbreak investigations. An important feature of care home environments is that they are semi-closed, meaning that one subset of the population stays within the care home, the residents, while another subset interacts with the community, the staff, and visitors. We measured the proportionate contribution of each transmission pathway into a completely susceptible care home, the role of population prevalence in causing outbreaks, and the breakout risk with baseline non-pharmaceutical interventions (NPIs) already in place.

I will present a continuous-time Markov chain model for disease transmission within and between care homes, together with a procedure for fitting this model to data obtained from temporal sampling of LTC facilities. This method is able to identify relative intensities of within and between care home transmission, generalising classic work using final-size data and more recent work that fits within-care home rates only.

DATA-DRIVEN MODEL REDUCTION FOR BIOMEDICAL DATA.

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In the realm of modern healthcare, the plethora of medical data available presents a unique opportunity for personalizing patient care. However, the practical utility of this data is often hindered by its multiscale, sparse, and sometimes incomplete nature. This underscores the need for robust mathematical models capable of encapsulating the diverse timescales inherent in the biomedical data. The multidimensional nature of these, along with their multiscalarity, call for the development of reduced order models which enable the efficient identification of patterns, patient-specific predictions, and therapeutic approaches. Central to these mathematical models and reduced order techniques is the approximation of a data-driven Jacobian matrix. In this work, we numerically approximate the Jacobian matrix of a deterministic SIS model using interpolation techniques and the Lyapunov Equation. Addressing scenarios with dense, sparse, or missing data, we employ regularization methods to estimate the mathematical models accurately. The validity of each approximation is rigorously evaluated against the system's analytical description. To derive a reduced order model, we employ the Computational Singular Perturbation method. The approximated Jacobians facilitate timescale decomposition, revealing dominant subprocesses and key variables. This approach offers a systematic methodology for developing data-driven models, elucidating the underlying mechanisms that govern the dynamics of biomedical data. This significantly contributes to the development of optimized, patient-specific models.

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EVOLUTIONARY GAMES WITH TIME DELAYS

Jacek Miekisz (University of Warsaw)

Time delays are ubiquitous in biological and socioeconomic processes. They usually lead to oscillatory behavior. Here we discuss other possible effects of time delays, not present in previously studied systems. We will present random walks with asymmetric time delays [1]. In such models, the probability of a system going to the right and to the left depends on the difference between two fitness functions in states of the system at two different times. The system exhibits new phenomena. Namely, the average position of a random walker (the expected value of the stationary probability distribution) depends on time delays. This is the combined effect of the system's stochasticity and time delays. In the deterministic version of the model, the walker moves along the cycle with an average value equal to the stationary point of the deterministic system without time delays. We have also observed that by an appropriate symmetric shift of fitness functions, we can reverse the effect of time delays. We will also discuss effects of strategy-dependent time delays in evolutionary dynamics of two-player games in finite populations (with logistic suppression) and in replicator dynamics of infinite populations. We compare our results to those in [2]. Our main result is that delays can be in certain circumstances beneficial. For example, delaying cooperative strategy may enhance the cooperation level in the population.

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OPTIMAL MANAGEMENT OF AN EMERGING PATHOGEN USING PRECAUTIONARY MANAGEMENT STRATEGY

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Other authors: Adam Kleczkowski

Emerging pests and pathogens have potentially devastating environmental, ecological and economic consequences, making their early control an imperative. There is an increased interest in designing Management strategies which reduce the rate of arrival of a pathogen ('precautionary' management) are frequently promoted as preferable. However, in practice, management strategies are often only deployed once an outbreak has been detected ('reactionary' management). With the frequency of pest outbreaks likely to increase, a key policy question is how to deploy resources to reduce their potentially irreversible impact. In this paper, we create a bioeconomic model to examine how the optimal level of precautionary management (which is restricted by a budget) changes when the key characteristics of the pest and its economic impact are changed. We show that when a reactive management strategy is unavailable, the optimal level of precautionary management increases as the primary and secondary disease transmission rates and the loss caused by disease. This trend still holds when a reactive management strategy is available, except for a small range of loss values where it is optimal to wait and deploy the reactive strategy only. Finally, we show that the optimal management strategy is highly sensitive to small changes in the effectiveness of both precautionary and reactive management.

MODELLING THE IMPORTATION DYNAMICS AND ESTABLISHMENT OF INFECTIOUS DISEASES USING A GENERAL BRANCHING PROCESS

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The invasion and subsequent establishment of novel pathogenic strains in a population is subject to a large degree of uncertainty due to the stochastic nature of the disease dynamics. Mathematical models need to take this stochasticity in the early phase of an outbreak in order to adequately capture the uncertainty in disease forecasts. We propose a general branching process model of disease spread that includes within-host level heterogeneity and a time-varying transmission rate, and that can be straightforwardly tailored to capture the salient aspects of a disease outbreak. We combine this with a model of case importation that occurs via an independent marked Poisson process.

We use this framework to investigate the impact of different control strategies, particularly on the time to establishment of an invading, exogenous strain. We also demonstrate the relationship between our model and a deterministic approximation, such that longer term projections can be generated that still incorporate the uncertainty from the early growth phase of the epidemic. Our approach produces meaningful short- and medium-term projections for a disease outbreak that are applicable in a wide variety of settings. These can be used by policy-makers, for example, to estimate the length time for which interventions need to be in place in order to achieve either local elimination of a disease or a delay in the time at which the disease becomes established in the population.

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MODELLING CELL ADAPTATION AND RESISTANCE USING INTERNAL VARIABLES: A CONTINUUM-BASED APPROACH FOR COMPUTATIONAL EPIGENETICS.

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Mathematical models are an essential complement to biological experiments, as they can help to better understand complex biological processes, test new hypotheses, and explore virtual situations which may be costly, complicated, or even impossible to test experimentally. In particular, in the last decades, many and varied mathematical models have arisen for the analysis and prediction of cancer evolution [1]. Phenomena such as epigenetics and cellular plasticity have a huge impact on cancer progression, as recently demonstrated in many biological studies [2]. Therefore, incorporating these features into mathematical models becomes paramount. Nevertheless, there are very few models which consider cell adaptation to the environment in a general and flexible way, most of them assuming the existence of a discrete number of cell phenotypes. This is far from the biological reality of gene expression mechanisms, i.e. epigenetics, which are too complex and uncertain to be reduced to a finite number of states and transitions between them. Inspired by the successful theory of internal variables in continuum mechanics as a common framework for explaining damage-reparation theory, viscoelasticity and plasticity, we propose the consideration of active advection fields. These fields represent the internal epigenetic state of the different cell populations, and, coupled with the transport of these populations, are able to reproduce the dynamics of epigenetic-driven tumors [3]. The framework allows incorporating cellular adaptation to the environment as well as the reversibility and inheritance of cell state. The use of internal variables enables a straightforward interpretation of the model structure and the use of mathematical tools from disciplines in which these models are widespread. In particular, the proposed model is able to reproduce the experimental trends found in the evolution and resistance to treatment of glioblastoma, the most common and lethal brain tumor.

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MINI-MODELS UNLEASHED: DECODING ZYGOTIC GENOME ACTIVATION IN ZEBRAFISH

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Zygotic genome activation (ZGA) is a crucial step in the development of various organisms, including flies, fish, frogs, and mammals, relying on pioneer-like transcription factors (TFs). These TFs facilitate the creation of open chromatin regions, enhance histone acetylation on enhancers, and trigger transcription. In this study, we utilize mathematical modeling, specifically mechanistic ordinary differential equation (ODE) models, to explore the complex interplay of TFs during ZGA.

Our investigation is grounded in data from single, double, and triple mutants of zebrafish genome activators Pou5f3, Sox19b, and Nanog, along with multi-omics data. Initially, we establish a transcriptional core model that accurately captures the dynamic behavior of pioneer-like TFs observed in different mutants. We then employ predictions from this core model to analyze how TF protein expression influences the regulation of 1800 genes during early zygotic development.

To accomplish this, we construct 19 small ODE models, termed mini-models, representing all possible combinations of TFs performing various regulatory roles. The mini-model that best aligns with available data for each gene is selected. The results of this analysis are cross-validated using an independent dataset measuring open chromatin regions.

Surprisingly, our findings indicate that Pou5f3 and Nanog exhibit both synergistic and antagonistic behavior, contrary to their previously assumed purely synergistic action, depending on the targeted gene. This underscores the complexity of TF interactions during ZGA and highlights the importance of mathematical modeling in unraveling these intricate regulatory mechanisms.

A NOVEL MODEL OF TUBERCULOSIS PROGRESSION USING COMPUCELL3D

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Tuberculosis (TB) is an airborne disease caused by the Mycobacterium tuberculosis (M. tb) pathogen. Prior to the COVID-19 pandemic, TB was the leading cause of death from an infectious agent globally. However, most people exposed to the M. tb pathogen do not develop active TB and become sick. Instead, the bacteria are typically contained within a granuloma, an aggregation of immune cells, without being eliminated; this is called latent TB. The spatial organisation of M. tb bacteria and immune cells is important in determining whether an individual exposed to the M. tb pathogen will develop latent or active TB.

In this talk, I present a spatiotemporal multi-cell, multiscale model of TB progression at the cellular level to investigate these hypotheses. I developed the model using CompuCell3D (CC3D), an open-source computer software used for simulating biological processes both within and between cells [1], and compared the generated results with those from a previously developed within-host infectious disease model [2]. I found that, although the results of my CC3D model mostly agree qualitatively with those from the previously developed model, there are quantitative differences. Additionally, I conducted a sensitivity analysis of key model parameters to determine their importance to the model output, using a methodology specifically designed for agent-based models [3]. The model output appears to be robust in response to perturbations of the parameter governing chemotactic bias, but less so in response to the parameter governing the contact energy between bacteria and macrophages. This talk will prove useful for researchers looking to build models using CC3D and will highlight the differences between this software and other agent-based modelling approaches.

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METHOD TO ESTIMATE THE IMPACT OF CONTROL MEASURES ON THE REPRODUCTION NUMBER

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At the start of the COVID-19 pandemic in early 2020, the SARS-CoV-2 virus could spread without any restrictions in a fully susceptible population. Soon control measures were taken to reduce contact rates, and immunity started to build up in the population. This resulted in a decrease of the reproduction number Rt, defined as the average number of secondary cases infected per primary case. If we know which part of this reduction can be attributed to the control measures and which part to immunity increase, we can estimate the impact of control measures on the reproduction number. Distinguishing between the two effects is complicated by heterogeneities in the population, especially between different age groups, that are not directly observable.

We propose an approximation method to attribute the reduction of the reproduction number to population immunity or contact rates. The method makes use of the properties of the next generation matrix, which describes the heterogeneity of virus transmission between age groups. The method requires incidence and immunity data by age group, but does not require any assumptions on the heterogeneities between age groups.

The proposed method is put to the test in a range of simulations, assessing the sensitivity to various structures of contact heterogeneity between age groups, waning of immunity, and age-dependent infectiousness and susceptibility. We will demonstrate that our approximation closely follows the exact solution, and only starts to deviate when the remaining susceptible fraction in the population is small.

Using this method the impact of control measures on the reproduction number can be evaluated over time.

THE EFFECT OF COMMUNITY STRUCTURE ON FIXATION PROCESS IN EVOLUTIONARY GRAPH THEORY

Javad Mohamadichamgavi (Institute of Applied Mathematics and Mechanics, University of Warsaw, Poland)
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Evolutionary dynamics and the success of mutants spreading through structured populations is an intriguing research domain. We construct a model consisting of two fully connected communities linked by a small number of connections as a kind of metapopulation where migration can happen through the connections between communities. Using an analytical Markov chain approach and simulations, we examine how the size of the initial mutant-arising community impacts fixation outcomes under a Moran birth-death process.

We discover that starting in a smaller community amplifies selection and increases fixation success compared to a larger community or well-mixed population. Specifically, when the size of the starting community is smaller than the second one, the population serves as an amplifier of selection. In contrast, initiating in a larger community suppresses selection success versus the neutral Moran expectation. Regarding fixation time, increased starting community size prolongs the conditional time until reaching a peak at a critical size dependent on fitness, after which declines. Unconditional time exhibits a more complex dependency on relative size and fitness interactions.

Our analytical approach assuming full takeover of the initial community before spreading matches well with simulations. By revealing the significant role of relative community sizes in shaping evolutionary outcomes, our work underscores accounting for population structure when modeling evolutionary dynamics. Our model provides a foundation to build more complex community-based population structures.

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A SIMULATION MODEL FOR PORCINE DISEASES IN A FARROW-TO-FINISH PIG FARM WITH INTRA-HERD TRANSMISSION THROUGH ANIMAL AND FARMER MOVEMENTS

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Other authors: M. Meester, O. Soriano, J. A. Stegeman, F. C. Velkers, T. J. Tobias, Y. Bahkshi, E. A. J. Fischer

A farrow-to-finish pig farm involves distinct groups of pigs in different life stages located across areas such as gestation (sows and gilts), lactation (sows and offspring), nursery (weaners), and fattening (finishers). Though areas are separated, pigs move between them based on pregnancy, age, or weight. while farmers move between areas during the day, creating pathways for disease transmission. Understanding the impact of these movements is crucial for disease management.

This study presents a disease model for farrow-to-finish farms, categorizing groups by life stages. The model integrates an SEIR framework with maternal immunity and environmental elements, adaptable to specific diseases. Emphasizing the farm's interconnected nature, the model incorporates both animal and farmer movements.

Simulations were conducted in EMULSION or Epidemiological Multi-Level Simulation Framework that facilitates the design and simulation of mechanistic stochastic models. It streamlines disease modeling without extensive code writing. Transmission parameters were estimated, covering within-group and between-group transmission, by Approximate Bayesian Computation via a Sequential Monte Carlo scheme (ABC-SMC) using the pyABC Python package.

To demonstrate the model applicability, it was applied to pig farm data from the Netherlands and Spain. In the Netherlands, data from an ongoing HEV study on fattening pigs was used with randomly generated movement data due to the lack of records. In Spain, syndromic data such as signs of respiratory symptoms was used including farmer movement data. These case studies showed the model's ability to simulate infection dynamics accurately in a farrow-to-finish farm after estimating the necessary transmission parameters.

In conclusion, this porcine disease model offers a nuanced perspective on the infectious disease dynamics in farrow-to-finish farms, providing valuable insights for effective disease management and biosecurity strategies

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A MATHEMATICAL APPROACH FOR TUMOR-ASSOCIATED MACROPHAGES IN GLIOMA GROWTH AND RESPONSE TO RADIATION

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Gliomas have been extensively studied using mathematical models that depict their longitudinal evolution over time as well as their spatial heterogeneity. However, most of these models have overlooked the role of the immune system in the tumor microenvironment—a network of ecological interactions that is crucial for the overall evolution of the tumor. Specifically, the population of tumor-associated macrophages (TAMs) can constitute up to 50% of the total cell count in human gliomas. In contrast to other immune populations, TAMs act as fuel for tumor cell proliferation, playing a necessary role in tumor growth and correlating with tumor aggressiveness. In order to describe these key interrelations, we developed an ordinary differential equation model for glioma growth that takes into account the feedback loops between tumor cells, brain microglia, and myeloid-derived macrophages. We used this model to fit the behavior of experimental data from mice. Furthermore, the response to radiation is affected by the presence of TAMs, and the effect of radiation alters the ecological ratios existing in the tumor. Consequently, we expanded our model to incorporate the effects of radiation therapy on the overall system and investigated the resulting changes in the tumor immune microenvironment. The model presented here sheds light on the complex interplay between different populations within the tumor microenvironment and might serve to design better radiation protocols and combination with radiosensitizers.

VIRAL KINETICS FOR EARLY INFECTION OF SARS-COV-2 AND RISK ANALYSIS

Jingsi Xu (University of Manchester)
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Interpreting viral mechanism of SARS-CoV-2 based on human body level is critical for developing more efficient interventions. Due to the limitation of data, limited models consider the viral dynamics of early phase of infection. In the Human Challenge Study (funded by the PROTECT national core study in transmission), each volunteer was inoculated by 10TCID50, of a wild type of virus, and the data indicates that the viral load reduced below the detectable level within a day, before eventually becoming detectable a few days later. We had previously developed a simplified within-host model that explains well the viral loads recorded during detectable viral activity. However, that model does not replicate the viral decay during early infection. In this presentation, I will introduce the original model we developed and expand it to introduce a new mechanism to explain this phenomenon based on the idea that the virus first goes through the adjustment phase and then starts to replicate. From this model the expected dose-response is derived to evaluate the probability of infection by constructing a boundary problem, which is then included in the fitting process by approximate Bayesian computation sequential Monte Carlo. Based on the results of parameter inference, we notice that the viral adjustment phase reduces exposed dose significantly.

Furthermore, we introduce models for early infection based on two alternative assumptions: the existence of an Allee effect (inhibiting viral replication at low density) or overwhelming of the innate immune response as viral grows. Our work indicates that both dose-response models have the same form as the cumulative distribution function of gamma distribution, which has not been systematically studied in the scope of dose-response models. And the consistency of these two dose-response models suggests that the Allee effect and boost of immunity mechanisms can have very similar effects on viral growth during the early infection.

CROSS-DISEASE PREDICTIVE ANALYSIS: A NEW PARADIGM IN PANDEMIC PREPAREDNESS

Joana Meyer (Institute of Comp. Biomedicine, RWTH)
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Pandemic preparedness has gained high relevance during the COVID-19 pandemic. Early-available predictive modeling is crucial for early disease management and decision support systems, yet it is challenged by the limited availability of disease-specific data and an incomplete understanding of disease mechanisms.

In this study, we propose a concept of rapid predictive modelling for novel diseases, based on the hypothesis that common disease-promoting mechanisms can be leveraged across different diseases.

We conducted a retrospective analysis on 6707 mechanically ventilated patients in intensive care units, including 495 cases of coronavirus. Rather than clustering patients by diseases, our model profiles cases based on disease progression using common monitoring parameters. This approach enables the translation of information gained from known diseases to novel diseases.

We observe that the accuracy of machine learning-based prognostic systems is impacted by rapidly evolving life-threatening events, such as septic shock, indicating a conceptual limitation in patient-specific outcome prediction. However, our model, focusing on common disease-promoting mechanisms and trained with non-COVID-19 patients, proved to be nearly as effective in predicting COVID-19 outcomes as models trained exclusively with COVID-19 data.

We advocate for the use of retrospective patient data repositories for translational learning based on common disease-driving mechanisms. This approach offers rapid strategy for predicting diseases outcomes of newly emerging diseases.

SYSTEMS BIOLOGY APPROACHES TO STUDYING SUBCELLULAR MECHANISMS AND THEIR REGULATION IN THE HUMAN PLATELET

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Platelets, small anucleate blood cells, play a vital protective function, aggregating to form a key component of blood clots that stop bleeding following vascular injury. In cardiovascular disease the same mechanism also triggers thrombosis, which can lead to heart attacks and strokes. Whilst many of the molecules involved in the intracellular processes that underpin platelet activation and aggregation have been identified, their specific roles in determining the rate and extent of the exceptionally rapid platelet response have yet to be determined. Understanding these complex molecular mechanisms is important for the development of more effective antithrombotic medicines.

We present a laboratory based, data-driven approach in which multiple mathematical models that are direct representations of biological knowledge and hypotheses regarding how intracellular mechanisms interact are derived from, and compared to, bespoke high-density quantitative data using a Bayesian framework. The predictions from these competing models have been used to direct new experimental set-ups that test model predictions and reduce non-identifiability. This approach has allowed the identification of how key therapeutic targets (Syk and Btk) within a platelet's GPVI pathway are regulated and how the associated mechanisms are conserved across species.

IDENTIFYING ENVIRONMENTAL AND ECOLOGICAL RISK FACTORS FOR HIGHLY PATHOGENIC AVIAN INFLUENZA IN WILD BIRDS

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The current epidemic of highly pathogenic avian influenza (HPAI) among wild birds is the largest on record. Wild birds form a reservoir for transmission of influenza to livestock, but the dynamics of HPAI in wild birds remains poorly understood. Previous studies have used species distribution models (SDMs) to predict the geospatial risk of HPAI by identifying relationships between specific environmental factors and the presence/absence of HPAI. In this study we expand upon existing SDM approaches to HPAI risk mapping by explicitly modelling the effect of ecological variables such as prevalence of HPAI host taxa, species richness, and diet preference. We use Bayesian additive regression trees, a non-parametric machine learning method, to model HPAI presence at a 10km resolution. We train our model using a Europe-wide dataset of over 8,000 geospatial records of HPAI from 53 wild bird families, adjusting for country-level sampling efforts using a random effects model. We optimise our model using 5-fold cross-validation and validate on outbreaks excluded from model training. Our projections align with current understanding in highlighting coastal regions and inland waterways as high-risk areas. Assessing variable importance reveals that altitude and temperature are important predictors of risk, consistent with previously published studies. Ecological variables including species richness and the prevalence of specific feeding behaviours improve model predictions, with their importance varying by season. Incorporating factors reflecting wild bird ecology improved the accuracy of our model relative to models which consider only environmental background factors and points the way towards future models using host species ecology in a disease ecology context. HPAI has important public health implications as a potential source of human pandemic influenza, and the models presented here offer a framework that could contribute to surveillance strategies for future HPAI epidemics.

THE POPULARITY SPECTRUM APPEARING IN CULTURAL EVOLUTION AND THE DIFFUSION APPROXIMATION

Joe Yuichiro Wakano (Meiji University)

We investigate a new approach for identifying the contribution of horizontal transmission between groups to cross-cultural similarity. This method can be applied to datasets that record the presence or absence of artefacts, or attributes thereof, in archaeological and ethnographic assemblages, from which popularity spectra can be constructed. Based on analytical and simulation models, we show that the form of such spectra is sensitive to horizontal transmission between groups. An analytically obtained spectra has a very complicated form, which can be approximated by a simple formula by using a specific diffusion limit. We then fit the analytical model to existing datasets and obtain evidence for strong horizontal transmission in oceanic as opposed to continental datasets. The implication for cultural evolution includes that functional traits may be more prone to borrowing than stylistic traits, although the current evidence for this remains ambiguous.

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A MATHEMATICAL MODELING APPROACH TO CLONAL ARCHITECTURE OF HEMATOPOIETIC CANCERS

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In cancers the underlying specific malignant clones are crucial for the development and success of potential treatments. The specific malignant mutation JAK2V617F is the most frequent mutation driving the slowly developing myeloproliferative neoplasms (MPNs). It is quite unlikely that both alleles in the DNA of a cell should be hit by the same mutation at the same time. First one allele mutates, and later mitotic recombination may transform heterozygous cells into homozygous cells by a probability p. The intrinsic properties are different, which has a large impact on treatment success. Homozygote cell fitness is approximately 1.2 times that of heterozygote cells [1] and clonal architecture of wild-type heterozygous and homozygous mutated cells - measured as clonal fractions (CFs) and variant alle frequency (VAF) - determines the response to treatment [2].

Based on [3] we posed an adjusted model describing the stem cells cycling between a niche-bound quiescent state, an autonomous active state, and a heteronomous partly inhibited state, where of the last two may differentiate into progenitors or attach to an empty niche. To account for zygosity three clones are considered, wild type, heterozygous cells, and homozygous cells, with possible transition from wild type to heterozygous cells and from heterozygous to homozygous cells. There is no direct competition between the clones, but they compete for empty niches. The model is calibrated to unique CFs- and VAF-data from Gustave Roussy, Paris, France and fit both ET, PV and PMF patient data well. The model offers understanding of which parameters differ between the clones as well as the impact of the niches for the dynamical development without treatment and with interferon-alpha treatment.

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OPTIMAL TIMING OF INTERVENTION AND TESTING FOR MITIGATING INFECTIOUS DISEASE OUTBREAKS IN PRISONS

Joseph Brooks (University of Manchester)
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Prisons present a unique environment for the spread of infectious diseases such as influenza, tuberculosis, and SARS-CoV-2: inmates have generally poorer health than average individuals of similar age; are generally confined in close proximity of each other, with regulated movements and interaction with staff often physical in nature; and their turnover constantly replenishes the susceptible population. Prisons are therefore highly vulnerable to new introductions, large outbreaks and significant disease burden. Although logistically difficult to manage, if no other options are available non-pharmaceutical interventions can be used in curbing the size and frequency of outbreaks within prisons, and have been used throughout the COVID-19 pandemic. Here we investigate specifically one of them, namely asymptomatic testing and isolation, and its potential impact in controlling infection spread in prisons. We consider an individual-based, stochastic, time-since-infection model, exploring several different infectivity profiles, to investigate how the concentration of infection load around its peak impacts the dynamics of the outbreak. We show how the timing of testing plays a crucial role in determining the efficacy of the intervention in reducing the final size or increasing the probability of extinction. Simulations reveal that profiles more concentrated around the peak infectious load exhibit more distinct generations of cases, with pronounced periodic patterns in the efficacy of the intervention as a function of the timings of its implementation. Conversely, in the case of more spread-out infection loads, earlier testing proved to be most effective, as the generations quickly overlap. Further considerations on model limitations, extensions and applicability to real-life scenarios, informed by a collaboration with public health stakeholders, will be discussed.

COUPLING PLANT PHYSIOLOGY AND PEST DEMOGRAPHY TO UNDERSTAND PLANT-NEMATODE INTERACTIONS

Joseph Penlap (Inria Center at Université Côte d'Azur)
Other authors: S. Touzeau, F. Grognard, V. Baldazzi

Root-knot nematodes (RKN) of the genus Meloidogyne spp. cause considerable yield losses in numerous crops worldwide. The dynamics and outcomes of crop–pest interactions depend on the ecological conditions, including the phenotypes of the interacting species, their physiology and the abiotic environment. In theoretical ecology, most mathematical models that describe these interactions either focus on plant physiology and do not consider pest dynamics, or conversely are based on the pest life cycle but neglect plant physiology and defense response. We are particularly interested in understanding the complex interplay between plant and nematodes.

To do this, we built a mechanistic model of plant-RKN interactions that explicitly couples plant physiology and pest demography, including both the known effect of pests on crop and crop on pests. Based on a mechanistic description of resource acquisition and transport, the plant model represents both vegetative and reproductive phase. The RKN model includes the free-living larval stage and the nematode development stages within the plant root. The model was calibrated on two plant species, tomato and pepper, with or without nematode inoculation. Model calibration is a challenge, as it relies on heterogeneous and fairly scarce data. Indeed, plant experiments focusing on roots are necessarily destructive, hence the scarcity of data and the need to incorporate data from different experimental sources. The model was then used to analyse the complex interplay between plant physiological traits, phenology and nematode biology that affects system dynamics. Eventually, the model will help to identify the plant traits that characterize susceptible and tolerant plants, opening new perspectives for varietal selection.

A HIERARCHICALLY STRUCTURED POPULATION MODEL WITH DELAY

Jozsef Farkas (Universitat Autonoma de Barcelona)
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In this talk I am going to introduce and study a hierarchical size-structured population model with delay. The model I discuss in involves two different types of nonlinearities. In particular it is assumed that growth and mortality are affected by scramble competition, while mating success by contest competition, hence the hierarchical structure. The qualitative behaviour of the model is analysed via linearisation using semigroup and spectral methods.

MATHEMATICAL MODELLING OF MECHANICAL COMMUNICATION BETWEEN CELLS

Juan Arellano-Tinto (Centre de Reserca Matemàtica)
Other authors: T. Alarcon, D. Stepanova, H. Byrne and P. Maini

Cell-cell communication is essential to coordinate cell migration in processes such as early development, blood vessel growth, and wound healing, among others. Cellular migration occurs within a complex, fibrous, and elastic environment called the extracellular Matrix (ECM), whose properties can play a significant role in coordinating and influencing cellular behavior over distances. The aim of this work is twofold: to analyse and quantify mechanical feedback resulting from cell-ECM interactions and to study cell crosstalk occurring at longer distances through these mechanical cues. In this work, we present an agent-based model that incorporates the main properties of cell-ECM interactions in a 2D framework. Cells are represented by polygonal shapes placed on an elastic substrate, with their interactions captured through mechanical forces. In addition, our model includes the dynamics of the attachment and detachment of focal adhesions, the complexes that mediate the interaction between cells and the ECM. This framework enables us to analyze the fiber alignment and strain transmission through the ECM between contracting cells for varying cell shapes (e.g. a round cell vs polarized geometry) and to describe characteristic force regimes for cells to detach from the ECM. Our model can be extended to account for cell migration and cell-ECM interactions in 3D, which are potential avenues for future work that we intend to pursue.

THE LIFSHITZ-SLYOZOV SYSTEM WITH INFLOW BOUDARY CONDITIONS

Juan Calvo (Universidad de Granada)
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The Lifshitz-Slyozov system describes the temporal evolutions of a mixture of monomers and aggregates, where monomers can attach to or detach from already existing aggregates. The aggregate distribution follows a transport equation with respect to a size variable, whose transport rates are copupled to the dynamics of monomers in a nonlocal fashion. Recent applications to protein polimerization phenomena introduce attachment and detachment rates that require a nonlinear boundary condition at zero size, which describes nucleation processes. In this talk we review and discuss the available results for this model concerning well-posedness and long-time dynamics, with a focus on those cases where concentration at small sizes is observed.

MODELING A RARE DISEASE: A CASE IN FIBROUS DYSPLASIA

Juan Carlos Beltran Vargas (Mathematical Oncology Laboratory (MOLAB), University of Castilla-La Mancha)

Most orphan diseases suffer from a lack of reliable data, making it difficult to determine their prevalence. However, biologists have made significant progress in developing methodologies and animal models for studying some of these diseases. Unfortunately, due to limited resources, research for orphan diseases is often not prioritized, which further exacerbates the scarcity of data available for analysis. In the absence or scarcity of data, mathematical models can play a crucial role, as they require less investment in experimentation compared to laboratory-based approaches. These mathematical models can provide valuable insights and bridge the gap in our understanding of orphan diseases. However, it is important to emphasize that a comprehensive understanding of the underlying biological processes is still essential for accurate modeling. In this oral presentation, a range of strategies will be presented for studying biological models and proposing their mathematical counterparts. The focus will be on Fibrous Dysplasia (FD) [1] as an illustrative example. FD is caused by a mutation in the GNAS complex [2], and by developing a simple mathematical model, intriguing hypotheses can be generated that have the potential to significantly enhance our understanding of the condition. By integrating biological [3] and mathematical approaches, researchers can leverage the strengths of both disciplines to overcome the challenges posed by orphan diseases. This interdisciplinary approach allows for a more comprehensive exploration of the mechanisms underlying these diseases, leading to novel insights and potentially guiding the development of new therapeutic strategies. Therefore, while orphan diseases often face limited resources and data availability, the combination of biological and mathematical modeling approaches can offer a promising avenue for advancing our understanding of these conditions.

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EFFECTS OF ANTIMICROBIAL DRUGS ON QUORUM SENSING DYNAMICS

Juan David Marmolejo Lozano (Universidad de los Andes)
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Quorum Sensing (QS) is a gene expression mechanism in response to population density, strongly linked to the virulence of bacterial infections. This study delves into the interplay between antibiotic treatments and QS dynamics, highlighting the potential implications for optimising antibiotic usage.

Utilising mathematical modelling and simulations, we explore the implications of periodic and oral antibiotic consumption during bacterial infection treatment. Such regimens influence gene expression dynamics, leading to fluctuations in population size and triggering environmental stress responses in the cells.

Our analysis delves into the repercussions on genetic networks, mRNA and protein concentrations, and noise in gene expression, intricately tied to bacterial persistence and resistance development. This research provides a comprehensive understanding of how antibiotic dosage and frequency might modulate QS and transcriptional networks governing toxin synthesis in a host.

Unraveling this relationship is crucial for optimising antibiotic usage, refining antibiotic administration, improving efficacy, and diminishing resistance and persistence risk. By elucidating the impact of antibiotic frequency and dosage on QS dynamics, our research aims to contribute to ultimately fostering sustainable antibiotic use against bacterial infections.

In conclusion, this study marks a significant step toward understanding the interplay between antibiotics and QS, offering insights that may reshape our approach to bacterial infection treatment. In an era where antibiotic resistance poses a formidable threat, unraveling gene expression dynamics in response to antimicrobial treatment is imperative for developing effective and enduring antibiotic strategies.

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INCORPORATING COMPLIANCE TO NON-PHARMACEUTICAL INTERVENTIONS IN EPIDEMIOLOGICAL MODELS

Ka Yin Leung (National Institute for Public Health and the Environment)
Other authors: J. Wallinga

During the COVID-19 pandemic, non-pharmaceutical interventions (NPIs) have been implemented to reduce transmission of infection. The transmission of infection is quantified by the reproduction number, the number of secondary cases per primary case. One would expect that at higher intensity of an NPI, the more effective the measure is in reducing the reproduction number, i.e. there is a monotone relation. Here we challenge this expectation. We focus on "stay-at-home requirements" as an NPI, specifically those that restrict the number of visitors per household. We study the impact of introducing this measure on the reproduction number and the infection attack rate at various intensities of an NPI. To this end we use a mathematical transmission model that allows for differences in compliance: a part of the population will comply to the measures and another part of the population will continue its contact behaviour irrespective of the measure. A reduction in contacts for the compliant sub-population always results in reduced average number of contacts in the entire population. However, an intervention measure of high intensity can be less effective in reducing the reproduction number than an intervention of moderate intensity. We show that such an unintended outcome is to be expected in more complex models as well. We argue that for some NPIs, similar outcomes can be expected. Moreover, we show that the epidemiological outcome of interest matters by showing that the infection attack rate in the compliant sub-population is relatively unaffected by the behaviour of the non-compliant sub-population. These findings highlight the importance of monitoring the actual compliance to measures, specifying the epidemiological outcomes of interest, and choosing appropriate NPIs given the level of compliance.

DYNAMIC ECM REMODELING DURING FORMATION OF TUMOR-ASSOCIATED COLLAGEN SIGNATURES

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Progression of benign breast cancer to an invasive tumor involves changes not only in the tumor cells, but also in the surrounding stroma, including modification in the extracellular matrix (ECM) fibril patterns. We used a combination of mathematical modeling (silicoDCIS model) and image analysis techniques to identify the rules of tumor cell-stroma interactions that guide the emergence of three tumor associated collagen signatures (TACS) previously observed in laboratory experiments. The TACSs are correlated with tumor behavior, such as benign growth or invasive migration, however, it is not fully understood how one specific fibril pattern can be dynamically remodeled to form another alignment. Here, we propose the rules of cell–ECM physical interplay and feedback that guided the emergence and transition among various TACSs. This integrated approach provides an in silico tool for testing biomechanical hypotheses of tumor cell-tumor matrix interactions that leads to tumor cell migration and formation of microinvasions.

IMPACT OF PREDATOR-DRIVEN ALLEE AND SPATIOTEMPORAL EFFECTS ON A SIMPLE PREDATOR-PREY MODEL

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In our present research article, we consider a Leslie-Gower reaction-diffusion model with a predator-driven Allee term in the prey population. We derive conditions for the existence of nontrivial solutions, uniform boundedness, local stability at co-existing equilibrium points, and Hopf bifurcation criteria from the temporal system. We identify sufficient conditions for Turing instability with no flux boundary condition for the spatial system. Our investigation delves into the analysis of diffusion-induced Turing instability, incorporating stability conditions for the constant steady state in the spatial model. We also investigate the conditions for the existence and non-existence of non-constant steady states in the diffusion-induced model. During numerical simulations, we observe that the predator-driven Allee term is essential for the model to generate Turing structures. Our findings reveal intriguing properties within the reaction-diffusion system, demonstrating its ability to produce patterns within the Turing domain. The simulation confirms that cold-hot spots and stripes-like patterns (a mixture of spots and strips) arise for different strengths of the predation parameter and Allee parameter. In contrast, we observe that for the above threshold value of the Allee parameter, the above-mentioned patterns may disappear from the system. Interestingly, we also observe that the stationary system produces patterns for both large and small amplitudes of perturbation in the vicinity of the Turing boundary. Our research may contribute valuable insights into the Allee effect and enhance our understanding of predator-prey interactions in naturalistic environments.

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CELLS ALIGN TO STRUCTURED COLLAGEN FIBRILS IN A HYBRID CELLULAR POTTS MODEL.

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The mechanical and chemical interactions between cells and their microenvironment plays an important role in understanding healthy and diseased tissue, including in embryonic development, tumor angiogenesis, and metastasis. A key component of the microenvironment is the so-called extracellular matrix (ECM). Here, we study how the local structure of the ECM is directly linked to cell morphology. To this end, we extend our previous, hybrid models of mechanical cell-ECM interactions [1] with a matrix consisting of discrete fibers and mechanosensitive focal adhesions. In vitro, when cells are put on oriented gels, they start aligning with the gel. It is observed that focal adhesions start forming around the poles of these elongated cells. We show how these focal adhesions can be the source of alignment of the cells due to the mechanical anisotropy that the orientation in the matrix creates. We have developed a hybrid cellular Potts model coupled to molecular dynamics model describing the ECM that incorporates discrete fibrous extracellular matrix and mechanosenstive focal adhesions. The model predicts that the stiffness sensing of the cell leads to cell spreading and to alignment of the cell to oriented matrices. With these two effects combined we study how ECM structure can determine cell morphology.

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A MATHEMATICAL MODEL ASSUMING FREQUENCY-DEPENDENT COST FOR ANALYZING THE INFLUENCE OF STEM CELL COMPETITION ON THE RADIATION EFFECTS

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The fact that high dose-rate ionizing radiation exposure increases the risk of cancer is well known, but the health effects of low dose-rate exposure are still controversial. The International Commission on Radiological Protection (ICRP) proposed a hypothesis that competitive elimination of radiation-damaged stem cells may contribute to the reduction of radiation effects under very low dose-rate rather than high dose-rate irradiation conditions. (Hendry et al. 2016). When the dose rate is very low, some cells are damaged and mix with intact cells. Then damaged cell may be eliminated through stem cell competition. Stem cell competition is a phenomenon in which stem cells with lower fitness are eliminated from the stem cell pool when they interact with neighboring stem cells with higher fitness. In this study, we developed a mathematical model to analyze the influence of radiation-induced stem cell competition on the accumulation of damaged cells. We assumed two types of cells: intact cell and damaged cell. The intact cell becomes the damaged cell by radiation exposure. Cell division and elimination follow the Moran process, where the probability of cell elimination depends on frequency-dependent cost. Under low dose-rate irradiation condition, the size of the cell pool could determine whether competition promotes or suppresses the accumulation of damaged cells, even when cost parameters were the same. In addition, we refine the model to explicitly consider the spatial structure and discuss how the results are affected when stem cell interactions are restricted to neighboring cells. When different types of cells having a higher cost affected neighboring cells, the results were qualitatively different compared to a scenario with no spatial structure. The considering spatial structure may be crucially important when discussing influence of stem cell competition in detail.

GROWING UP AND FEELING LIKE A LOSER. IMPACT OF MATURATION DELAY ON THE ECO-EVOLUTIONARY DYNAMICS OF ZERO SUM GAMES IN CHANGING ENVIRONMENT.

Krzysztof Argasinski (University of Warsaw, Department of Mathematics)
Other authors: Jacek Miekisz

The talk will present the results from two unpublished papers, continuing the previous work on demographic evolutionary games by Argasinski and Broom (2018a, 2018b). The demographic approach assumes that, instead of a single payoff function describing Darwinian fitness, there are two payoff functions describing births and deaths. This approach allows for the introduction of different forms of density-dependent population size regulation, such as juvenile recruitment survival probability.

We will begin by presenting the updated demographic payoff functions, taking into account the explicit probabilities of winning/losing during conflicts with a particular strategy. The updated structure of the payoff functions is more suitable for describing zero-sum games than the approach from previous papers. Additionally, the existing conditions for eco-evolutionary stability will be completed by the introduction of so-called subnullclines - surfaces connecting stable and unstable restpoints, attracting trajectories before they reach the stable restpoint.

Next, we will extend the modeling framework by adding maturation delay for newborns. This implies the application of delay differential equations. The resulting models are very sensitive to the influence of external factors, as demonstrated by adding the seasonal mortality factor or explicit predator pressure modeled by a simple Lotka-Volterra system. Numerical simulations of the obtained models exhibit very complex behavior, including complicated oscillations and cycles, or even chaos. One of the surprising results is that in some cases the impact of the delay vanishes in the negihbourhood of subnullclines.

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ESTIMATING THE RISK OF VECTOR-BORNE DISEASE SPREAD IN SEASONAL ENVIRONMENTS

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Other authors: W.S. Son, A.Y. Lim, D.U. Hwang

The risk of vector-borne disease transmission is affected by climate conditions as it influences the vector and pathogen development processes and the disease transmission risk in a tick-host cycle. In this study, we developed an approach to assess the time-varying reproduction numbers of P. vivax malaria, while considering the influence of seasonal factors on the generation interval. These seasonal factors include mosquito abundance as well as the pathogen latency within humans and mosquitoes. As an example, the vector abundance for P. vivax malaria in South Korea is highly seasonal, and it affects the time of transmission which happens upon a mosquito bite and consequently affects the generation interval. With the developed model, we estimate the reproduction numbers of P. vivax malaria utilizing weekly data on mosquito abundance, temperature, and symptom onset from three bordering regions in South Korea. Specifically, we computed two distinct types of reproduction numbers - the case reproduction number and the instantaneous reproduction number. We demonstrate that the two measures can be utilized to provide insights into the risk of malaria transmission in endemic regions and identify the time of the year at which individuals who develop symptoms contribute most significantly to the transmission.

A DELAYED MODEL FOR TUMOR-IMMUNE SYSTEM INTERACTIONS

Laid Boudjellal (CMAT, University of Minho)
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Advances in mathematical modeling can enable to understand the interactions among cancer cells and cells of the immune system and their response to treatment, thereby promoting the progress towards targeted and effective therapies for this highly complex disease.

According to [1] and references therein cited, the tumor-immune system interactions can be summarized in three relevant phases, namely: the clearance phase, the equilibrium phase, and the escape phase. In particular, during the escape phase, tumor cells exhibit an accelerated expansion and growth than in other phases. Moreover, one of the most effective immunotherapy that helps immune system against tumor cells during the escape phase is the adoptive cellular therapy. For that reason, our main interest is studying the dynamical behavior of tumor-immune cells interactions during this critical escape phase.

Starting from our previous ODE model, we propose a delay differential equations model that describes the rivalry among tumor and immune cells in the presence of adoptive cells therapy and interleukin. The delay is incorporated in the model to represent the time lag by the adaptive immune cells for responding after recognizing the tumor cells. The delay introduces some complexities on the dynamics but has the novelty of capturing the memory of the cells [3]. For the delay model, we prove the consistency between the model solution and the biological context, including existence, uniqueness, positivity and boundedness of the solution. We study the stability of the equilibrium states, and investigate the existence of bifurcations in the parameter space. We complement our study with various numerical simulations that show different behaviors of the solution. Finally, we compare the results obtained for the delay model with those for the ODE model in order to evaluate the effect of the time delay on the dynamics.

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COUPLED ENVIRONMENTAL AND DEMOGRAPHIC FLUCTUATIONS SHAPE THE EVOLUTION OF COOPERATIVE ANTIMICROBIAL RESISTANCE

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Other authors: M. Asker, A. M. Rucklidge, M. Mobilia.

Antimicrobial resistance is a global threat responsible for millions of deaths [1]. There is a pressing need to better understand how microbial populations respond to antimicrobial drugs, and to find mechanisms to possibly eradicate antimicrobial-resistant cells. The inactivation of antimicrobials by resistant microbes can often be viewed as a cooperative behavior leading to the coexistence of resistant and sensitive cells in large populations and static environments. This picture is however greatly altered by the fluctuations arising in volatile environments, in which microbial communities commonly evolve. In this presentation I will discuss the eco-evolutionary dynamics of a population consisting of an antimicrobial resistant strain and microbes sensitive to antimicrobial drugs in a time-fluctuating environment, modeled by a carrying capacity randomly switching between states of abundance and scarcity [2, 3] (https://eedfp.com/). We assume that antimicrobial resistance is a shared public good when the total number of resistant cells exceeds a certain threshold, which fully inactivates the antimicrobial drug and protects sensitive cells. Eco-evolutionary dynamics is thus characterized by demographic noise (birth and death events) coupled to environmental fluctuations that can cause population bottlenecks. By combining analytical and computational means, we determine the environmental conditions for the long-lived coexistence and fixation of both strains, and characterize a fluctuation-driven antimicrobial resistance eradication mechanism, where resistant microbes experience bottlenecks leading to extinction. Finally, I will discuss the possible applications of our findings to laboratory-controlled experiments and drug-treatments.

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EPIBEDS: DATA-INFORMED SHORT-TERM PROJECTIONS OF THE COVID-19 HOSPITAL AND CARE HOME BURDEN IN THE UK

Lorenzo Pellis (The University of Manchester)
Other authors: Feng Xu, Christopher Overton, Helena B. Stage, Francesca Scarabel, Katrina Lythgoe, Thomas House, Ian Hall

The COVID-19 pandemic has put considerable strain on national healthcare systems and care homes worldwide. Immediately after the first lockdown in March 2020, researchers involved in modelling advice in support of the UK pandemic response were asked to develop models to provide short-term projections of epidemic spread and hospital burden, and estimates of the effective reproduction number (Re). Later on in the pandemic, care homes also needed to assess how well testing and other internal control measures had performed in limiting the impact of COVID-19 in those critical settings.

We developed a deterministic compartmental model of infection spread, coupled with a detailed description of progression through hospital and critical care. A partially complete patient-pathway line-list was used for the most appropriate, data-driven, choice of the hospital compartments and to provide initial estimates of the transition rates between them. Using MCMC and a negative-binomial likelihood, we then fitted the model to complete time-series data on hospital admission, hospital and ICU bed occupancy, and hospital deaths. This enabled generation of short-term projections for all four data streams and estimation of COVID-19 severity in hospital, measured as the proportion of individuals that follow different clinical pathways during the different pandemic waves. The model was then extended to include age stratification and additionally fitted to deaths outside of hospitals, virtually all concentrated in care homes, to track the infection burden in these settings.

The most interesting and novel aspects of the model will be discussed, with particular focus on practical data issues, model limitations, and the advantages of a simple and transparent model over complex ones. Projections and Re estimates from this model have been produced weekly throughout the pandemic for England (and the regions therein), Wales, Scotland and Northern Ireland, and combined with other models to

SPIKE-ADDING PHENOMENA IN BURSTING MODELS: DISSECTING THE BIFURCATION SKELETON

Lucía Pérez (University of Oviedo)
Other authors: R. Barrio, S. Ibáñez, S. Serrano

Bursting is a dynamical behavior characterized by the alternation between periods of rest and oscillations in the magnitude of a given system. Examples include the electrical activity of neurons, pancreatic β-cells, and the dynamics of certain lasers and chemical reactions. In the context of bursting, spike-adding refers to the creation of new spikes in the bursting trains. Two common types of bursting are fold/hom bursting and fold/Hopf bursting.

In this study, our goal is to comprehend the spike-adding phenomena in models exhibiting fold/hom and fold/Hopf bursting activity. We focus on the Sherman-Rinzel-Keizer model, a biophysically detailed representation of a pancreatic β-cell. We elucidate the role of bifurcation structures, particularly homoclinic bifurcations, in organizing different spike-adding processes.

Previous research analyzed the Hindmarsh-Rose model, a phenomenological, polynomial model of neuronal activity, proposing a global scheme that locates spike-adding processes with respect to the homoclinic structure. In our work, we demonstrate that this global scheme is not exclusive to the Hindmarsh-Rose model but may be applicable to a broader range of fold/Hom bursting systems.

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THE WOLVERINE AND REINDEER: ON THE ROLE OF PREY SENESCENCE IN PREDATOR-PREY DYNAMICS

Ludek Berec (University of South Bohemia, Czechia)

Predator-prey relationships are focal to ecological research, and often their exploration needs more than a classic, unstructured predator-prey model. Imagine a prey population composed of juveniles, adults, and a non-reproductive class of elderly, and predators that preferentially consume more easily accessible young and old prey. In theory, presence of the latter group may have both positive and negative effects on population dynamics (or individual fitness). On the positive side, old conspecifics may help raise young or protect them from predators, directly via group defense or indirectly via serving as a valuable food source. On the negative side, the old compete with at least the adults for food and contribute to transmitting infections if there are any. Here we model these complex and conflicting effects of the elderly and study their impact on population dynamics, switching on and off those various mechanisms. Also, we let the average time spent in the elderly class be an evolutionary trait and examine its evolution via adaptive dynamics. Alternatively, we assume that the predator may scavenge in addition to killing prey, and study evolution of its degree of scavenging.

MODELLING OF ECOLOGY INTERACTIONS IN A PHOTOTROPHIC-HETEROTROPHIC BIOFILM REACTOR SYSTEM

Luigi Frunzo (University of Naples "Federico II")
Other authors: M. R. Mattei, A. Tenore

The presentation will concerns a mathematical model for the analysis and prediction of microbial interactions within mixotrophic biofilms composed of microalgae and heterotrophic bacteria. The model combines equations for biomasses growth and decay, diffusion-reaction of substrates, and detachment process. In particular, the colonization of external species invading the biofilm is considered. The biofilm growth is governed by nonlinear hyperbolic PDEs while substrate and invading species dynamics are dominated by semilinear parabolic PDEs. It follows a complex system of PDEs on a free boundary domain. The equations are numerically integrated by using the method of characteristics. The model has been applied to simulate the ecology of a mixotrophic biofilm formed by phototrophic and heterotrophic species. The comparison of numerical and experimental data will confirm the accuracy of the proposed model.

DELAYED LOSS OF STABILITY OF PERIODIC TRAVELLING WAVES AFFECTS WAVELENGTH CHANGES OF PATTERNED ECOSYSTEMS

Lukas Eigentler (University of Warwick)
Other authors: M. Sensi

Many patterned ecosystems, such as dryland vegetation patterns and intertidal mussel beds can be described by PDEs admitting periodic travelling waves (PTWs). Under a changing environment that increases stress, such systems undergo a cascade of wavelength changes before an extinction event occurs. Classically, wavelength changes have been predicted by identifying the intersection of a PTW's wavelength contour with a stability boundary in the system's Busse balloon. In this talk, I highlight that this information is often insufficient because of a delayed loss of stability phenomenon. I show that PTWs can persist as transients for ecologically significant times after the crossing of a stability boundary in the Busse balloon. I present a method that can predict the order of magnitude of the time delay between the crossing of a stability boundary and the occurrence of a wavelength change by linking the delay to features of the essential spectra of the PTWs.

GROWTH, ENERGY, OR BOTH? DETERMINANTS OF OPTIMAL METABOLIC PATHWAY CHOICE BY MICROORGANISMS

Maarten Droste (VU Amsterdam)
Other authors: R. Planqué, F. J. Bruggeman

Microbial growth and physiology are often studied from the perspective of maximization of the specific growth rate, as this enables one species to outcompete others through natural selection. This viewpoint allows for translation to a mathematical modeling framework that can describe growth of single-celled organisms in terms of optimal metabolic strategies. These strategies allocate limited resources amongst the internal processes in the most efficient way. As microbes adapt their behavior due to intra- and extracellular factors, we investigate what determines their optimal strategy. In this talk, we will explore this question using thermodynamics.

Thermodynamics considers a population of growing microbes as an open out-of-equilibrium system. With this approach the metabolic network can be studied as a black box, converting energy and matter from its environment into biomass and waste products. We use these concepts together with optimality principles to understand the role of thermodynamics in determining the best strategy of the organism. We will consider both abiotic environments, where external transport of metabolites is governed by diffusion, and cross-feeding interactions that can change the optimal behavior.

Systems considered in physics often have a positive flux-force relationship, showing an increase in flux as the corresponding driving force increases. For continuous culture growth conditions, we study the relation between the thermodynamic driving force and the growth rate for yeast. We show that metabolic shifts can break the positive flux-force relationship, which could result in non-increasing entropy production rate as function of growth rate. Hence, living systems may obey different principles than those that are inanimate.

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INVESTIGATING SPATIAL SIGNATURES OF EXTRACHROMOSOMAL DNA IN CANCER WITH AGENT-BASED MODELLING

Magnus Haughey (Queen Mary University of London)
Other authors: I. Noorani, B. Werner.

Extrachromosomal DNA (ecDNA) are small circular DNA elements which, in cancers, often contain important oncogenes and regulatory regions. EcDNA is observed across many cancer types and is associated with poor patient outcome [1] yet its formation, maintenance and role in cancer development is poorly understood. Existing mathematical models of ecDNA in cancer have neglected spatial constraints during tumour growth [2], but these effects could significantly alter the evolutionary path of the tumour. Here we summarise recent advances, driven by spatial computational modelling, which exploit spatially resolved measurements of ecDNA in human tumours to investigate their role during tumourigenesis and reveal some of the underlying dynamical rules governing the interplay between ecDNA and tumour cells during cancer growth. We present the first theoretical exploration into how spatial constraints during tumour growth, coupled to non-Mendelian inheritance of ecDNA fragments, drive high oncogene copy numbers in these tumours. These spatial effects can also act to preserve small populations of tumour cells lacking ecDNA fragments: a phenomenon with potentially important implications for resistance to targeted therapy. Next, by combining our model framework with multi-region measurements of ecDNA copy numbers in human glioblastoma multiforme, we explore how to optimally utilise the spatial context of tissue samples to understand ecDNA dynamics in vivo. We estimate, on a patient-specific basis, the number of ecDNA copies in the tumour initiating cell, the strength of spatial constraints acting on cells during tumour growth, and the impact of ecDNA presence on cell fitness. In doing so we uncover trends in evolutionary dynamics for different ecDNA-amplified oncogenes. Combined, these results demonstrate the knowledge which can be gained by leveraging the spatial context of cells and provide a baseline for future spatial analyses of ecDNA driven cancers.

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MATHEMATICAL MODELING OF WILD TYPE AND MUTANT KERATIN-14 NETWORK DYNAMICS AND KERATIN AGGREGATE FORMATION

Marcos Gouveia (CFisUC - Center for Physics of the University of Coimbra)
Other authors: T. Sorčan, Š. Zemljič-Jokhadar, R. Travasso, M. Lović

The intermediate filament cytoskeleton is responsible for the mechanical integrity of the cell, as well as protecting it from external stress. Intermediate filaments are fibers that can form complex networks located in the cytoplasm and the disruption the keratin cycle of assembly/turnover, can lead to fragility of the skin, leading to diseases such as Epidermolysis Bullosa Simplex (EBS). The keratin cycle is a highly dynamic process that starts from the nucleation of keratin unit-length-filaments (ULFs) near the cell cortex. These proto-filaments are transported by the actin fibers towards the nucleus, where they start to disassemble and monomers diffuse towards the cell cortex, where the cycle restarts. It has been shown that in the case where mutant keratin is present, the formation of filaments is scarce, and instead we see the appearance of keratin granules near the cell membrane. Further studies on the origin of these aggregates suggest that they contain both wild-type and mutant keratin and their amount is maximum for cells with a 25% mutant keratin fraction. In order to reproduce the spatial distribution of keratin in a cell, we created a mathematical model that couples a phase field model for the cell and its nucleus, with a system of PDEs for the concentration of keratin in different states. To understand how the amount of aggregates depends on the fraction of mutant keratin in the cell, we use a system's biology approach, suggesting a system of coupled ODEs that describes the dynamics of both wild-type and mutant keratin, in different forms. We found that we are able to reproduce the spatial distribution of keratin observed in vitro, in the case where a filament network is formed and also when there is the appearance of aggregates. We show that by assuming aggregates are formed by the asymmetric binding of wild type and mutant keratin, we are able to predict that maximum amount of aggregates occurs for cells with a 25% mutant keratin content.

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THE SYNERGISTIC INTERPLAY BETWEEN AMYLOID BETA AND TAU IN ALZHEIMER'S DISEASE: A MATHEMATICAL MODEL ON THE HUMAN CONNECTOME

Maria Carla Tesi (University of Bologna)
Other authors: M. Bertsch, S. Bianchi, B. Franchi, G. Landi, C. Testa, V. Tora

Toxic proteins such as Beta-amyloid (Abeta) and Tau play a crucial role in the development of Alzheimer's disease (AD) and, separately, have been targets of medical treatments. Recent biomedical literature stresses the potential impact of the synergistic action of these proteins. In this talk I will present a mathematical model for the progression of AD in the human brain. The novelty of the approach consists in the representation of the brain as two superposed graphs where toxic proteins diffuse, the connectivity graph which represents the neural network on which Tau diffuses, and the proximity graph, which takes into account the extracellular space, on which Abeta diffuses. The calibration of the model is performed via a detailed statistical analysis of medical data (stuctural MRI and Tau-PET) from ADNI datasets. With the model appropriately calibrated, we numerically test various modelling hypotheses which confirm the relevance of the synergy.

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CARDIOMYOCYTES' SIGNAL PROPAGATION ON THIN DOMAINS IN THE KARMA MODEL

Maria Elena Gonzalez Herrero (TU Munich)
Other authors: C. Kühn

The questions if and how electrical signals propagate along heart tissue are key to decide if the organ can sustain a healthy beat or not. To understand better what factors could either help or disrupt this propagation we study a polynomial version of the Karma model, specifically developed to fit cardiomyocytes' behaviour well while maintaining the advantages of a low-dimensional model similar to FitzHugh-Nagumo. On the real line we analytically derived a stable travelling pulse supporting important properties of cardiac electrical pulses using phase plane analysis and geometric singular perturbation theory [M. E. Gonzalez Herrero, C. Kühn, K. Tsaneva-Atanasova, (2021)]. Nevertheless, to be able to compare the mathematical results to experimental data, we need to extend the problem to a more realistic finite 2-dimensional domain. With our work we aim to prove when and how we can approximate the problem of signal propagation on a thin 2D tissue by a 1-dimensional pulse. For that we use the method of matched asymptotics to approximate the solution. Depending on how we define the limit between 2D to 1D and the interaction of this limit with the multiple time scales intrinsic to the model, the approximation strategies needed and the corresponding solutions differ. Therefore, we do not find one unique expansion but instead a family of separate asymptotic regimes, each with a corresponding approximation. Finally, using direct numerical simulations we compare and connect different initial conditions to the asymptotic regimes found in the analysis in the hope to understand how this family of approximations comes together to represent the full system.

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ON THE EXACT AND POPULATION BI-DIMENSIONAL REPRODUCTION NUMBERS IN A STOCHASTIC SVIR MODEL WITH IMPERFECT VACCINE

María Gamboa Pérez & Maria Jesus Lopez-Herrero (Complutense University of Madrid)

In this talk we aim to quantify the spread of a direct contact infectious disease that confers permanent immunity after recovery, within a non-isolated finite and homogeneous population. Prior to the onset of the infection and to prevent the spread of this disease, a proportion of individuals was vaccinated. But the administered vaccine is imperfect and can fail, which implies that some vaccinated individuals get the infection when being in contact with infectious individuals. We study the evolution of the epidemic process over time in terms of a continuous-time Markov chain, which represents a general SIR model with an additional compartment for vaccinated individuals. In our stochastic framework, we study two bi-dimensional variables recording infection events, produced by a single infectious individual or by the whole infected group, taking into account if the newly infected individual was previously vaccinated or not. Theoretical schemes and recursive algorithms are presented in order to compute joint probability mass functions and factorial moments for these random variables. We show the applicability of our techniques by means of a set of numerical experiments.

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MODELLING GENE TRANSFER AND BACTERIAL RESISTANCE IN BIOFILMS

Maria Rosaria Mattei (University of Naples Federico II)
Other authors: J. Vincent, A. Tenore, L. Frunzo

The global spread of antibiotic microbial resistance (AMR) is an increasing health concern, and has been mainly attributed to antibiotics abuse and misuse. Dissemination of AMR is largely associated to plasmids, extra-chromosomal genetic elements. Plasmid-carried resistance is transferred to new host cells through conjugation, which plays a crucial role in the ecological success of plasmids in bacterial communities. We present a mathematical model simulating the social behaviour of bacteria in biofilms regulating plasmid transfer under selective pressure from metals or co-resistance and cross-resistance to antibiotics and metals. The model is formulated as a free boundary problem for a nonlocal system of PDEs with a convolution integral modelling the regulation of transfer genes expression. Gene expression is modelled as depending on the presence of potential receptors around a donor, called recipient-sensing. Dynamics of nutrients and metals is governed by reaction-diffusion PDEs. A promotion function is also introduced to account for the metal stimulation or inhibition on conjugation. Numerical simulations showed that the model is able to qualitatively reproduce the influence of conjugation on plasmid dynamics in a growing biofilm. In particular, the relative influence of conjugation and vertical gene transfer was compared, including the selective pressure exerted by the metals.

ACCURATE AND EFFICIENT INTEGRATION OF WITHIN-HOST MODELS INTO DISCRETE STOCHASTIC POPULATION MODELS OF INFECTIOUS DISEASES.

Mark B Flegg (Monash University, Australia)
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Compartment models of infectious diseases are often modelled using differential equations. In the case where small numbers or noise play an important role in the model outcomes, differential equations are replaced with Markovian models where discrete individuals are members of a compartment and transition stochastically. These stochastic models are often memoryless. For example, an assumption of the model may be that all members of an infected class behave the same. When more high-resolution information about infected individuals is required, within-host viral dynamics of individuals should be integrated with the population model. This poses several challenges computationally by breaking the memoryless property of traditional stochastic methods. We explore novel ways of addressing this challenge in this seminar.

INTERDIGITATION BETWEEN IN SILICO SINOATRIAL AND ATRIAL CELLS IMPROVES THE ROBUSTNESS OF CONDUCTING ACTION POTENTIALS

Martijn de Jong (Mathematical institute, Leiden University)
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The heartbeat is initiated by electrical pulses generated by a specialized patch of cells called the sinoatrial node (SAN), located on top of the right upper chamber, and then passed on to the atrium. Cardiac arrhythmias may arise if these electrical pulses fail to propagate toward the atrial cells. The SAN exhibits a higher resting potential than the surrounding right atrium. The negative potential of the atrium may suppress the pacemaker activity of the SAN if the electrical coupling between atrial cells is too strong. However, if this coupling is too weak, the pacemaker cells cannot activate the atrial cells due to a source-sink mismatch. The SAN balances these two extremes by being fully insulated, except for several specialized conduction pathways [1]. Within these pathways, the SAN and atrium form interdigitating structures [2] that are hypothesized to contribute to the robustness of pulse propagation by providing a transition region between the cell types. We have investigated this interdigitation hypothesis using a hybrid cellular Potts and partial-differential equation model. The former model initializes the cellular morphology whereas the latter simulates the electrophysiology as a reaction-diffusion equation. We investigated in detail how the model parameters affected the pulse propagation between the SAN and the atrium. By systematically analyzing how the morphological characteristics of interdigitation patterns affect the probability of an exit block, we find that a symmetric geometry with medium-sized protrusions can prevent exit blocks. Built-up current in small protrusions leaks to the atrium quickly, whereas curvature effects are lacking with large protrusions. Current work focuses on the morphogenesis of interdigitating patterns using a genetic algorithm and testing our model with in vitro monolayer experiments. Overall, we have provided design principles that can aid in vitro experiments and help understand the occurrence of exit blocks in vivo.

[1] Fedorov, V.V. et al. (2010). Optical Mapping of the Isolated Coronary-Perfused Human Sinus Node. Journal of the American College of Cardiology, 56(17), 1386-1394. https://doi.org/10.1016/j.jacc.2010.03.098

HYBRID EPIDEMIOLOGICAL MODELS FOR EFFICIENT INSIGHT ON THE INDIVIDUAL SCALE: A CONTRIBUTION TO GREEN COMPUTING

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Mathematical modeling has been proven to be of great aid for many different domains by complementing classical physical experiments. A large variety of models has already helped to create a better understanding of physical, biological, or epidemiological processes. As infectious disease dynamics are highly driven by heterogeneous human contact patterns and human behavior, agent based models are most suitable to investigate underlying structures and to generate insights into individual-scale properties. However, the additionally gained knowledge has to be paid by a huge computational effort as the complexity grows linearly or quadratically with the number of considered agents inside a region or location [1]. In our paper, we show how hybrid epidemiological models can reduce the computational effort by more than 90 % without losing the required depth in information on the individual scale. In order to keep the computational effort small, agent based models are often only developed for a region or time-frame of interest, e.g., neglecting information from coupled regions. By using well established metapopulation models for coupled regions or time-windows with less stochastic influence, agent-based model predictions can be improved and individual-scale information of the focus area can be retained without substantial increase in effort or energy consumption. Although nowadays, high-perfomance computing (HPC) techniques allow the simulation of increasingly large problems, HPC also produces increasingly large CO2 footprints. Hybrid epidemiological models can complement software and hardware optimizations to reduce energy consumption by only computing the necessary level of detail where needed, using dynamically developing summary statistics where possible. In this talk, we will briefly explain the temporal and spatial hybrid models and then present results of a spatial hybrid model for the city of Munich and its neighboring or connecting counties.

QUANTIFYING THE EFFECTS OF NON-PHARMACEUTICAL INTERVENTIONS IN A COMPARTMENTAL EPIDEMIOLOGICAL MODEL

Marvin Schulte (Fraunhofer Institute for Industrial Mathematics ITWM)

Throughout the COVID-19 pandemic, numerous non-pharmaceutical interventions (NPIs) were implemented to mitigate disease spread by reducing human interaction. In compartmental epidemiological models, human interaction is typically represented by a parameter known as the critical contact rate or simply contact rate. Furthermore, different testing strategies, together with the quarantine of infected individuals, have been applied in order to reduce disease spread. The question arises which quantitative effect the NPIs have on the contact rate and which detection rate can be assumed for different testing strategies.

To study this effect, we will first describe the epidemiological model used. In contrast to classical SEIR models, we assume an averaged fixed time for the onset and end of infectiousness. This leads to a system of delay differential equations. The model also allows for age-stratification. Briefly, we will show how we incorporated the effects of multiple virus variants with partial immune escape into the model.

Using data from federal states of Germany, we will calibrtate our model parameters, particularly time-dependent contact and detection rates, to achieve the best accordance with data in a long-term simulation. By comparing these parameters to different NPIs and testing strategies in German federal states, we quantify the respective effects.

Finally, we will discuss how the quantification of such measures can help us to find an optimal strategy during a pandemic. This strategy can include NPIs, (mass) testing and vaccination. We will state the mathematical formulation for this optimization problem.

INVESTIGATING THE IMPACT OF DISEASE ON ABORIGINAL AUSTRALIA WITH STOCHASTIC MULTI-PATCH EPIDEMIC MODELS

Matthew C. Nitschke (Global Ecology Laboratory, Flinders University)
Other authors: C. J. A. Bradshaw, F. Saltre

Smallpox was unknown to the indigenous populations of the isolated continent of Australia. This was one of the most damaging of new infectious diseases to break out among Aboriginal Australians when their isolation came to an end. However, very little is known about the pre-colonial population of Australia and the impact of novel diseases. This has fueled speculation about the origin of these outbreaks that began soon after the arrival of the first permanent European settlers. By the time these settlers arrived in 1788, the indigenous inhabitants of Australia had developed a very complex culture with over 390 distinct language groups spread across a diverse landscape. To account for this heterogeneity, we divide the continent into patches according to the geographical range of these groups, each of which have a different risk of infection determined by connectivity of the group and natural geographical boundaries. Incorporating these differences, we present a stochastic multipatch epidemic model to simulate how smallpox may have spread through the continent and investigate the effect it had on the resident population.

ASSESSING THE COUPLED EFFECTS OF FISHING PRESSURE AND CLIMATE CHANGE ON WEST GREENLAND'S ECOSYSTEM USING AN END-TO-END ECOSYSTEM MODEL

Matthew Hatton (University of Strathclyde)
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The West of Greenland is at the forefront of anthropogenic climate change. The loss of sea-ice and the freshening of polar water is placing the food web at risk of disruption, endangering food security and cultural heritage for indigenous communities [Anastario et al. 2022; Ford et al. 2012].

Here we present an approach to exploring the coupled effects of increased fishing pressure and climate change using the end-to-end ecosystem model, StrathE2EPolar. StrathE2EPolar is driven by output from the NEMO-MEDUSA earth system model and aims to represent the entire food web from macro to megafauna, alongside the associated environment.

This research seeks to address how fishing pressure may function analogously to an amplifier, potentially intensifying the impacts of climate change. In addition, we investigate how specific aspects of the ecosystem, such as biomass of certain taxa and productivity at low to high trophic levels, could be influenced by the interaction between climate change and fishing. Moreover, maximum sustainable yields are compared for climate scenarios in the present day and the 2040s decadal period, exploring the even greater effect that fishing practices could have on the ecosystem if the current pattern of climate alterations persist.

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[2] Ford, J.D., Pearce, T. (2012). Climate change vulnerability and adaptation research focusing on the Inuit subsistence sector in Canada: Directions for future research. Canadian Geographies / Géographies canadiennes, 56(2), 275-287.
https://doi.org/10.1111/j.1541-0064.2012.00418.x

SARS-COV-2 EVOLUTION ON A DYNAMIC IMMUNE LANDSCAPE

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Since the onset of the pandemic, many SARS-CoV-2 variants have emerged, exhibiting substantial evolution in the virus' spike protein, the main target of neutralizing antibodies. A plausible hypothesis proposes that the virus evolves to evade antibody-mediated neutralization (vaccine- or infection-induced) to maximize its ability to infect an immunologically experienced population. While virus infection induces neutralizing antibodies, viral evolution may thus navigate on a dynamic immune landscape that resulted from a local infection history. Global inequalities in vaccine distribution and differences in infection-prevention measures have shaped this immunological landscape, resulting in uneven geographic distributions of SARS-CoV-2 variants. Consequently, predicting which variants will spread within particular regions has become increasingly challenging. To tackle this challenge, we developed a comprehensive mechanistic model of the dynamic immunological landscape of SARS-CoV-2. We utilized deep-mutational scanning data and antibody pharmacokinetics to compute time-dependent cross-neutralization between arbitrary variants. Combined with infection history and molecular surveillance data, we could predict the variant-specific relative number of susceptibles over time. This quantity precisely matched historical variant dynamics, predicted future variant dynamics, and could explain global differences in variant dynamics. The model can be applied to any region by utilizing local genomic surveillance data. Our work strongly supports the hypothesis that SARS-CoV-2 evolution is driven by escape from humoral immunity, allows contextualizing risk assessment of variants, and provides important clues for vaccine design.

[1] von Kleist, M. (2023). SARS-CoV-2 Evolution on a Dynamic Immune Landscape. Research Square. https://doi.org/10.21203/rs.3.rs-3366919/v1

MATHEMATICAL MODELING UNVEILS OPTIMIZATION STRATEGIES FOR TARGETED RADIONUCLIDE THERAPY OF BLOOD CANCERS

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Targeted radionuclide therapy (TRT) is based on intravenous injections of cancer-specific antibodies conjugated with radioactive nuclides. Despite its specificity, TRT is harmful for rapidly proliferating organs, well perfused by blood, like bone marrow. We developed a mathematical model based on our experiments on multiple myeloma mouse model treated by 225Ac-DOTA-daratumumab. Its study yielded the following insights on TRT optimization.

Labeling Ratio Importance. The use of standard labeling ratio yields 1800 unlabeled antibodies per one radioconjugate. Due to occupation of receptors by unlabeled antibodies, average multiple myeloma cell attracts only 70 nuclides, which decays can be insufficient to yield lethal damage.

Proper Dosing Strategy. Cancer shields healthy organs by attracting drug from blood. Effective rate of this process depends on cancer binding capacity, i.e., total number of its specific receptors. This provides basis for personalized dosing strategy, that can be performed during a single visit. Injection of a small diagnostic dose and measurement of its pharmacokinetic curve allows for estimation of cancer binding capacity. The number of injected antibodies in the following therapeutic dose should be 1.5 times greater than it, unless there is a risk that the backflush of radioactive remnants from dead cells to blood is unacceptably toxic, which can be assessed based on physiological ranges of pharmacokinetic parameters.

Prolonged Alpha-Particles Administration. Once cancer binding capacity is near saturation, further injected radioconjugates are redirected to yet undamaged cells, which continue producing specific receptors. In case of prolonged administration of emitters of short-range alpha-particles, the deposited dose is as well redirected towards viable cells, that promotes treatment efficacy. However, low number of remaining free receptors leads to effective drug dilution, as greater fraction of nuclides decays before binding.

MULTISTATIONARITY FOR N-SITE MIXED PHOSPHORYLATION NETWORK

Maya Mincheva (Northern Illinois University)

Multisite phosphorylation is an important mechanism in cellular biology associated with protein function. Mathematical models of mono- and dual- site phosphorylation networks have been studied recently, while less research is available on multisite phosphorylation. Phosphorylation networks could be processive, distributive or mixed where the phosphorylation or dephosphorylation occurs through a combination of both mechanisms. Parametric dynamical systems representing multisite phosphorylation networks are often multistationary, which means that they have several positive steady states. We analyze a dynamical system of a mixed n-site phosphorylation network for multistationarity. A general algebraic condition in the form of a simple inequality which determines a multistationary parameter region is obtained.

QUANTIFYING THE STOCHASTIC DYNAMICS OF TRANSCRIPTION-COUPLED DNA REPAIR

Michael Nicholson (CRUK Scotland Centre, Institute of Genetics and Cancer, University of Edinburgh)

Other authors: C. Anderson, D. T. Odom, S. J. Aitken, M. S. Taylor

DNA base damage is a major source of cancer-causing mutations and disruption to gene expression. Transcription-coupled repair (TCR) minimises the risk of damage within genes, but experimental measurement of this DNA repair process is challenging. Here, we combined a well powered murine model of cancer development with a stochastic model of damage and repair to quantify the mechanisms of TCR on DNA alkylation adducts. We show that RNA-polymerases frequently bypass lesions without triggering repair, indicating that small alkylation adducts are unlikely to be an efficient barrier to gene expression but are likely to be a source of mutant RNA. The efficiency of TCR gradually decays through gene bodies leading to a rejection of the standard conceptual model that transcription immediately resumes after repair. Our results have implications for the accurate inference of driver mutations in cancer and the effects of DNA damage on expression, especially for genes with a large genomic span.

INTEGRATED UNDERSTANDING OF HUMAN PGCLC DEVELOPMENT USING MULTI-SCALE MATHEMATICAL MODELING OF GENE-CELL-BMP DYNAMICS

Michito Ujino (Kyoto University, ASHBi)
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Understanding of germ cell fate is one of the most challenging problems in biology and medicine. Primordial Germ Cell (PGC) is the origin of germ cell lineage, which differentiate into spermatozoa or oocytes. Recently, many extracellular morphogenic substances, such as BMP, and genetic regulatory networks required for PGC development have been identified by experiments. However, the spatial effect of BMP distribution is still poorly understood in the dynamics of germ cell differentiation. To understand the mechanism of germ cell development and its relationship with BMP integrally, we developed a multi-scale mathematical model composed of genetic/transcriptomic networks of ordinary differential equations (ODE), stochastic model for differentiation decision, and BMP-individual cell interaction model of partial differential equation (PDE) combining discrete cellular dynamics. The models have been constructed based on the scRNA-seq data and other experimental data. Using the model, we tested several scenarios of BMP concentrations on germ cell development and confirmed that GATA3 commit to differentiation earlier, as shown in experiments. In addition, we conducted sensitivity analysis to investigate the essential genetic network pathways for PGC development and found that GATA3 related pathway is essential for PGC development, as shown in the experiment of GATA3 knockout that significantly impaired PGC development. With the model verification based on the results above, we finally explored the spatial effect of BMP on PGC development through in silico experiments using the multi-scale model of PGC development. In this study, we show that the spatial pattern of BMP is crucial for efficient production of PGCs and propose a new in vitro experiment framework for PGC manipulation based on gene-cell-BMP dynamics.

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ANALYSIS OF THE DYNAMICS BETWEEN BACTERIA AND PHAGES

Miller Cerón Gómez (Universidad de Nariño)

We investigate the stability of a mathematical model describing the interaction between a Bacterial pathogen and Bacteriophages. We have identified two thresholds to characterize the dynamics of the coexistence equilibrium and phage extinction equilibrium. Additionally, we found the existence of a Hopf bifurcation.

[1] Beke, G., Stano, M., Klucar, L. (2016). Modelling the interaction between bacteriophages and their bacterial hosts. Mathematical Biosciences (279): 27-32.
https://doi.org/10.1016/j.mbs.2016.06.009

ESTIMATING UNREPORTED CONTACT PATTERNS IN KOREA FROM EMPIRICAL DATA USING A HYBRID MODEL

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In June 2023, the Korean government had declared the end of the COVID-19 emergency and gradually lifted the restrictions to prevent the spread of the disease. In line with this, individual intention has become an important factor in the prevention of the disease, and therefore, in the mathematical modelling of the epidemic. Since, as described in the previous study [1], the intention is strongly dependent on the epidemic risk perception, the perception need to be considered as one of the epidemic parameters in the modelling. There are several previous researches to consider risk perception in the epidemic modelling, however, most of the modelling resort to assumptions about perception levels that are not estimated by the real data [2]. To address this limitation, we propose an epidemic forecasting model using the risk perception estimated from internet search data on COVID-19. The model is a hybrid of a deep learning model and a compartment model. The deep learning model uses a graph attention neural network (GAT) and long-short term memory (LSTM) to infer the epidemic risk perception. With this inference, the probability of preventive behavior is calculated and used to estimate the epidemic parameter in the compartment model. Since the proposed model can be utilized to check how the risk perception changes the epidemic dynamics, it can be used as a basis for determining the future epidemic policy in terms of public perception. Furthermore, this model can reveal unreported COVID-19 confirmed cases. We tested the proposed model on the data collected from the Korean representative search engine (i.e., NAVER). As a result, the model achieved high prediction accuracy and successfully identified the unreported cases.

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[2] Verelst, F., Willem, L., Beutels, P. (2016). Behavioural change models for infectious disease transmission: a systematic review (2010–2015). Journal of The Royal Society Interface, 13(125), 20160820. https://doi.org/10.1098/rsif.2016.0820

MATHEMATICAL MODELING OF SUBUNIT FORMATION IN PEX14

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Peroxisomes are dynamic organelles and essential for health and development. The enzymes acting in peroxisomes have to be imported via a multi-protein machinery. Pex14 is a component of the import machinery complex and studies have indicated that the ability of Pex14 to form homo-oligomers is important for an efficient import process. We measured the subunit formation in Pex14 and developed a mathematical model to analyse the exchange of monomers, dimers and trimers. With help of the model we were able to determine time-scales of the exchange process and analyse the fluxes between the different species. The experimental data used for the modeling is measured with native MS and each species has a different response factor. The determination of response factors is an often unconsidered and challenging task and analysis via dynamic modeling could be a promising strategy. Via observation functions the model was used to determine the different response factors out of the data and the found values are in good agreement with existing results.

MATHEMATICAL AND NUMERICAL ANALYSIS OF TURING PATTERNS IN BIOLOGICAL SYSTEM FOR NODAL AND LEFTY.

Mohamed Amine Ouchdiri (Mohammed VI Polytechnic University)
Other authors: S.Benjelloun, A.Saoud and I Otero-Muras.

In this study, we conduct a detailed mathematical and numerical analysis of the first synthetic mammalian reaction diffusion circuit, addressing the Nodal and Lefty signaling pathway [1]. In this system, Nodal acts as a short-range activator whereas Lefty as a long-range inhibitor. Leading to the formation of spatial patterns.

Initially, we begin by establishing that the model of the parabolic system of Partial differential equations, is well posed, ensuring that there is a unique global and bounded solution in time. The linear stability analysis shows that the model can exhibit various patterns such as stripes, hexagons and other self-organized structures [2], via Turing driven instability.

We suggest that these patterns variation result from different bifurcation types, with the self-organized structures due to a strong subcriticality regime provided by the model in a specific range of kinetics. We deepen our mathematical analysis using a weakly non-linear multiple scales approach [3] to characterize different types of Turing bifurcation, both supercritical and subcritical.

Our analysis provides a mathematical explanation of the variety of complex Patterns observed experimentally or numerically. Finally, we conclude our presentation with methods for efficient control strategies for Nodal/Lefty signaling pathway.

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PHASE FIELD MODEL FOR CELL SPREADING DYNAMICS

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We suggest a 3D phase field model to describe 3D cell spreading on a flat substrate. The model is a simplified version of a minimal model that was developed in [1]. Our model couples the order parameter u with the actin network's 3D polarization (orientation) vector field P. We derive a closed integro-differential equation governing the 3D cell spreading dynamics on a flat substrate, which includes the normal velocity of the membrane, curvature, volume relaxation rate, a function determined by the molecular effects of the subcell level, and the adhesion effect. This equation is easily solved numerically. The results are in agreement with the early fast phase observed experimentally in [2]. Also we find agreement with the universal power law [3] which suggest that cell adhesion or contact area versus time behave as $\sim t^{1/2}$ in the early stage of cell spreading dynamics, and slow down at the next stages.

MATHEMATICAL MODELING OF PHOSPHATE KINETICS FOR HEMODIALYSIS

Morten Andersen (Roskilde University)
Other authors: K. O. Bangsgaard, JG Heaf, JT Ottesen.

Chronic kidney diseases imply an ongoing need to remove toxins, with hemodialysis as the preferred treatment modality. We derive analytical expressions for phosphate clearance during dialysis, the single pass (SP) model corresponding to a standard clinical hemodialysis and the multi pass (MP) model, where dialysate is recycled and therefore makes a smaller clinical setting possible such as a transportable dialysis suitcase. For both cases we show that the convective contribution to the dialysate is negligible for the phosphate kinetics and derive simpler expressions. The SP and MP models are calibrated to clinical data of ten patients showing consistency between the models and provide estimates of the kinetic parameters. Immediately after dialysis a rebound effect is observed. We derive a simple formula describing this effect which is valid both posterior to SP or MP dialysis. The analytical formulas provide explanations to observations of previous clinical studies. The work is based on an interdisciplinary collaboration between mathematicians and a nephrologist and I will touch upon the benefits and challenges of such a collaboration.

LONG-TERM IMPACT OF VACCINATION ON THE ANTIGENIC EVOLUTION OF RNA VIRUSES

Myrthe Willemsen (UMC Utrecht)
Other authors: I. M. Rouzine, G. Rozhnova

RNA viruses rapidly evolve to evade antibody-mediated immunity. This antigenic evolution contributes to re-infection and recurrent epidemics. Vaccination has been recently hypothesized to intensify selective pressure and accelerate antigenic escape relative to natural infection at the population level [1]. We explored the long-term impact of vaccination on the epidemiological dynamics and speed of antigenic evolution.

We extended a strain-based evolutionary model [2] to include periodic vaccination. A set of integrodifferential equations describe individuals infected or recovered with specific virus strains. Viral evolution is caused by stochastic mutations in the antibody-binding regions embedded in a one-dimensional antigenic-strain space. Susceptibility increases with the antigenic distance between the infecting and last encountered strain. Vaccination decreases susceptibility in synergy with this natural immune memory. We evaluated the impact of the vaccination frequency, strain and coverage on the infection density and evolutionary speed, the displacement in antigenic space over time, using Monte Carlo simulations.

In the scenario without vaccination, parameterised to seasonal influenza, the model demonstrates a traveling wave in the antigenic space and fluctuations over time around a steady-state density of infectious individuals. Vaccination with high coverages and frequencies reduces the infection density and amplifies fluctuations, as well as causes a phase transition between stochastic and periodic oscillations. Permitting for reinfection with the same strains sharply boosts infection densities and reduces fluctuations.

We also investigate the robustness of results to assumptions regarding the single-strain immune memory, the dimensionality of antigenic space, and functions governing cross-immunity. We compare our predictions with available data of influenza and SARS-CoV-2.

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[2] Rouzine, I. M., Rozhnova, G. (2018). Antigenic evolution of viruses in host populations. PLOS Pathogens, 14(9), e1007291. https://doi.org/10.1371/journal.ppat.1007291

MODELLING THE EVOLUTION OF SYMBIOSIS IN THE CONTEXT OF EUKARYOGENESIS

Nandakishor Krishnan (Eötvös Loránd University, Budapest)

The evolution of eukaryotes from symbiosis between ancestral prokaryotes is considered a major evolutionary transition. The initial interactions and conditions that enabled such obligate symbiosis and eventually led to the formation of a new level of organism are widely debated. The Syntrophy hypothesis based on metabolic utilization is one of the prevalent theories explaining the basis of the formation of intimate associations. We present a possible evolutionary path toward an association between two unicellular species based on unidirectional syntrophy. In our efforts to understand this mechanism, we develop a mathematical model in which we hypothesize that the first step in the evolution of such symbiosis could be the appearance and invasion of a mutant phenotype into a monomorphic resident system stabilized by syntrophy. We investigate the ecological and evolutionary stability of the symbiotic association (or consortium). The dynamics of the population densities of the involved species are represented using a set of non-linear ordinary differential equations, and the growth rates of each species are represented using novel Malthusian functions based on a branching process. We observed that a mutant host capable of metabolic inhibition (shielding from toxic metabolite) and a highly metabolically active mutant symbiont could independently initiate ectosymbiosis even if the mutants incur additional costs relative to the residents. Our model of ectosymbiosis could be a precursor to the events of endosymbiosis.

INFERRING CORNEAL EPITHELIAL CELL BEHAVIOUR FROM A MATHEMATICAL MODEL

Neda Khodabakhsh Joniani (University of Sydney)

The cornea is the outermost transparent layer of the eye arranged in several layers. Unlike many epithelial tissues that only have one layer, the corneal epithelium, which is the cornea's exterior surface, is composed of 5-7 stratified layers. This stratification occurs through a process known as cell delamination whereby cells from one layer move upwards to the layer above. Furthermore, the corneal epithelium is preserved by migration of new basal cells from the periphery, where they are produced by stem cells, to the centre of the cornea. In 2016, Lobo et al., used mathematical and biological models to show that corneal epithelial cells in the basal layer have a centripetal growth pattern. However, given that corneal epithelium is multilayered, there are some open questions: What regulates this stratification and how are the layers organized?

In this talk, we present an agent-based model including biological forces and feedback to describe cell behavior in the basal layer. Additionally, we proposed an approach to capture the dynamics of cell delamination from the basal layer.

[1] Lobo, E.P. et al. (2016). Self-organized centripetal movement of corneal epithelium in the absence of external cues. Nature Communications, 7(1). https://doi.org/10.1038/ncomms12388

BIRTH-DEATH PROCESSES FOR MODELLING BACTERIAL HETERORESISTANCE UNDER ANTIMICROBIAL STRESS WITH SUBSTRATE UTILISATION KINETICS

Nerea Martínez López (Byosistem & Bioprocess Engineering Group (IIM-CSIC))
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Antimicrobial Resistance (AMR) in bacteria is emerging as a critical health concern worldwide and as one of the most complex challenges for mathematical biology. Experimentation with Population Analysis Profiling or Etests has revealed different AMR levels within the same isogenic population, leading to subpopulations with different antimicrobial responses. This phenomenon, called heteroresistance, further complicates the dynamics of AMR emergence, transmission and selection. For example, more resistant bacteria may survive the antimicrobial treatment and regrow in the long term but also mediate in horizontal transfer by conferring AMR to the sensitive subpopulations (e.g. through plasmids). Nevertheless, despite its undesirable implications in treating bacterial infections, there is a lack of predictive mathematical models explaining bacterial heteroresistance.

In this work, we propose a new mathematical model of bacterial heteroresistance. We introduce the AMR level in the model as an independent variable characterising the antimicrobial response and model each subpopulation with a (stochastic) birth-death process. Thus, each bacterium divides and dies randomly at rates depending on its AMR level, allowing for spontaneous modifications augmenting or diminishing AMR (e.g. gene amplifications). The per-cell division rate and the AMR level are related through the substrate utilisation parameter, taking into account the AMR fitness cost, which causes the cell to lose its efficiency as AMR increases. We propose flexible Hill-type dependencies for the birth-death-modification rates on the AMR level and the antimicrobial concentration, assuming a bactericide effect (the substance kills bacteria but does not impede cell division). The resulting heteroresistance model is identifiable from realistic time-kill data, demonstrating its practical utility for calibrating the parameters and the heteroresistance distribution uniquely from measurements of total cell counts.

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EFFICACY OF THE STERILE INSECT TECHNIQUE IN PRESENCE OF INACCESSIBLE AREAS: A STUDY USING TWO-PATCH MODELS

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The Sterile Insect Technique (SIT) is one of the sustainable strategies for the control of disease vectors, which consists of releasing sterilized males that will mate with the wild females, resulting in a reduction and, eventually a local elimination, of the wild population. Implementing the SIT in the field can become problematic when there are inaccessible areas where the release of sterile insects cannot be carried out directly. The migration of wild insects from these areas to the treated zone may influence the efficacy of this technique. On the other hand, one can also take advantage of the fact that released sterile males can circulate between the two zones. Our main question is whether we can control the populations in both areas while only releasing sterile insects in one zone. In this paper, we derive a two-patch model for the Aedes mosquito population that are vectors of many arboviruses such as yellow fever, dengue, zika, and chikungunya. The dynamics on each patch are described by a monotone dynamical system in which the population is divided into different compartments characterizing the aquatic phase, wild females, wild males, and sterile males. We use a discrete diffusion to model the movement between the treated patch and the inaccessible patch. We investigate in this work two different release strategies: constant and impulsive periodic releases. Using the monotonicity of the model, we show that if the number of released sterile males exceeds some threshold, the technique succeeds in driving the whole population in both areas to extinction. We also show that the threshold depends not only on the biological parameters of the population but also on the diffusion rates between the two patches.

DERIVATION AND NUMERICAL STUDY OF A FOKKER-PLANCK EQUATION DESCRIBING A POPULATION OF RESONATE AND FIRE NEURONS

Nicolas Zadeh (ULB)

The well-known Integrate and fire model in a partial differential equation (PDE) form has been at the center of many mathematical developments since Brunel's work and the seminal paper by Caceres et al in 2011. Its descriptive shortcomings such as the inability to see sub-threshold oscillations or to obtain resonances gave birth to the resonate and fire model (Izhikevich, 2001), phenomenologically complex enough but computationally not costly .

However, there has been no deep mathematical study of it yet. In this work, we first establish a PDE corresponding to the mean-field limit of a population of resonate and fire neurons. We then discuss the expected behavior coming from this model.

The obtained formulation corresponds to a non-linear kinetic Fokker-Planck equation, with a non-local linearity and a measure source term, studied on a half plane. Considering the difficulty of obtaining explicit solutions as well as the complexity of the kinetic theory, we study it numerically.

We thereby obtain a finite differences positivity and mass preserving scheme of experimental order one, which allows us to observe all the properties we were expecting from the original single neuron model, and even giving birth to some conjectures which we shall detail.

The author would like to deeply thank Guillaume Dujardin (INRIA Lille) and Pierre Roux (Ecole Centrale de Lyon) for their invaluable help on this work.

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ON THE ROLE OF DELETERIOUS MUTATIONS IN LONG-TERM 63 2 3 EVOLUTION

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Birth-death models have long been employed to understand the interplay of genetic drift and natural selection. While well-mixed populations are insensitive to the choice of the individual type for replacement−parent or offspring– this choice strongly influences the evolutionary outcomes for spatially structured populations. Moving parent individuals to vacant sites gives rise to new update rules, leading to new fixation categories for spatial graphs. We discover a new category of graphs, amplifiers of fixation, where a structure has a higher probability of fixation for mutants than the well-mixed population, regardless of its fitness value. Under death-Birth updating with parents moving to vacant sites, the star graph is an amplifier of fixation. For very large population sizes, the fixation probability to fix deleterious mutants on the star graph converges to a non-zero value, contradicting the result from well-mixed populations where the probability goes to zero. Additionally, most random graphs are amplifiers of fixation for death-Birth updating, with parent individuals replacing dead individuals. Conversely, most random graphs are suppressors of fixation– graphs with lower fixation probability for mutants regardless of their fitnesses– for Birth-death updating with offspring replacing dead individuals. When subjected to long-term evolution, amplifiers of fixation, despite being more efficient at fixing beneficial mutants, attain lower fitness than the well-mixed population, whereas suppressors attain higher fitness despite their inferior ability to fix beneficial mutants. These surprising findings can be explained by their deleterious mutant regime. Therefore, the deleterious mutant regime is equally crucial as the beneficial mutant regime for adaptive evolution.

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EFFECTIVE STOCHASTIC SIMULATION OF ADAPTATIVE NETWORKS IN EPIDEMIOLOGY

Nils Gubela (Freie Universität Berlin)

Modelling and simulation of the spread of pathogens has proven to be crucial to inform containment strategies and cost effectiveness calculations. Pathogen spread is often modelled as a stochastic process driven by pathogen exposure on time-evolving contact networks. In adaptive networks, not only does the spread process depend on the dynamics of a contact network, but conversely, infection dynamics can change risk behaviour and thus feed back on contact dynamics, leading to emergent complex dynamics. There are no analytical solutions for this class of inhomogeneous stochastic processes, and numerically exact simulation is computationally prohibitive. In this talk, we use the example of estimating the efficacy of HIV pre-exposure prophylaxis on a sexual contact network to illustrate the various computational bottlenecks. We discuss exact and inexact rejection-based strategies for simulating the spread of the pathogen in the evolving network. We provide error bounds and overhead estimates for all methods. We also discuss variance reduction sampling methods, which lead to a decrease in computational effort and help us to estimate parameter sensitivities.

MANAGING BIOFILM INFECTION THROUGH CONTROLLED DRUG RELEASE FROM A POLYMER-FREE IMPLANT

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In the realm of implant-associated infections, understanding and controlling biofilm formation is paramount. Surface-bound bacterial communities knows as biofilms, evolves through stages such as initial attachment, stabilisation through extracellular polymeric substance (EPS) production, and development of different bacterial phenotypes such as proliferative, persister and dead cells, and finally possible detachment. Single-species biofilms are typically associated with medical implant infection and treating these infections is challenging due to the biofilm's resistance to antibiotics, compounded by issues like nutrient deficiency and low oxygen in deeper biofilm layers. Our study presents a mathematical model to understand how biofilms react to varying antibiotic doses and release rates at the implant-biofilm interface, aiming to refine targeted drug treatments.

Our one-dimensional model for biofilm growth allows for controlled antibiotic release from polymer-free, nano-porous implant and includes different bacterial phenotypes, EPS, nutrient levels, biofilm water content and biofilm growth, providing a novel perspective in the design and development of biomedical implants to counteract infection [1, 2]. This model has already advanced our understanding of effective drug delivery, considering factors like nutrient availability, the development of bacterial phenotypes and both natural and antibiotic-induced bacterial mortality. Notably, as antibiotic doses increase, the density of proliferative bacteria decreases, and persister bacteria increases, similar to experimentally observed antibiotic resistance. Our next goal is to identify the optimum antibiotic administration method to eliminate both the infection and these resilient cells, preventing further implant infections which will improve patient outcomes through better-informed surgical practices and implant selections.

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MODELING AND CONTROL OF TUMOR GROWTH: ALTERNATIVE APPROACHES

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The application of mathematical modeling to understand and control tumor growth and treatment is crucial for exploring the impacts of anti-tumor drugs and designing effective personalized therapies. While traditional approaches often rely on mechanism-based methods for constructing tumor models, an innovative alternative, based on the formalism of Chemical Reaction Networks (CRN), has been recently introduced. This study extends the CRN-based approach to offer a dual characterization—both deterministic and stochastic—of the system. This dual perspective proves valuable for addressing diverse research questions. The advantage of the CRN lies in its seamless translation into both stochastic and deterministic frameworks. Stochastic modeling, exploiting the Chemical Master Equation (CME) tool, captures the inherent random fluctuations in the chemical interactions within the network. On the other hand, deterministic modeling, employing ordinary differential equation (ODE) models, provides linear approximations of the average dynamics derived from the CMEs. This dual approach is applied to a minimally parameterized, low-dimensional model of tumor growth and treatment. Through numerical simulations, it is demonstrated that the deterministic framework is well-suited for characterizing system behavior when the number of tumor cells is significantly high, enabling the design of deterministic control strategies. Specifically, two deterministic control approaches are analyzed: the first involves constant drug administration, while the second employs a state-feedback control scheme with either complete or partial knowledge of the system state. The results obtained show the advantages and limitations of both strategies, emphasizing the crucial role of the initial tumor size in determining treatment outcomes.

MEAN FIRST PASSAGE TIME AND ITS APPLICATION IN OCULAR DRUG DEVELOPMENT

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Standard of care for various retinal diseases involves recurrent intravitreal injections. This motivates mathematical modelling efforts to identify influential factors for drug residence time, aiming to minimise the administration frequency. To this end, we developed a mean first passage time (MFPT) modelling framework, to investigate the scaling relationships of ocular pharmacokinetics in humans and animal species and to inform drug development.

The MFPT describes how long it takes, on average, for a random walker to reach a given target, and is a valuable method to quantify the efficacy of diffusion transport. In this work, we derived a partial differential equation system for the MFPT to quantify drug residence time, and solved it in detailed anatomical 3D geometries of eyes of animal species used in drug development assessments. For human eyes, we investigated the impact of variability in vitreous cavity size and eccentricity, and in injection location, on drug elimination.

Model simulations revealed a dependence of residence time on ocular size and injection location. Inter-individual variability in human eyes had a significant influence on residence time (half-life range of 5-7 days), showing a strong correlation to axial length and vitreal volume. The modelling results suggest that experimental variability in ocular half-life is partially attributed to anatomical differences and injection site location.

PREDICTING THE TIME TO RELAPSE FOR INDIVIDUAL PATIENTS WITH GLIOBLASTOMA FOR THE SECOND-LINE OF INTERVENTION

Pejman Shojaee (Teschniche Universität Dresden)
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Glioblastoma is one of the deadliest central nervous system (CNS) cancers, with few significant therapeutic advances in the past few decades, leading to a median survival of only about 15 months despite aggressive conventional therapy. The behavior of cells at their invasive front is crucial for the clinical progression and the quality of life of patients. Additionally, the prediction of tumor behavior or the time frame for recurrence post-surgery is challenging, owing to the tumor's highly heterogeneous nature and the abundance of clinical data. The accuracy in predicting clinical outcomes for this condition is hindered by two main issues: first, a limited understanding of the fundamental mechanisms controlling the data variables, and second, inadequate data collection resulting from dependence on the patient's clinical symptoms. The first issue affects the precision of mechanistic models and precise underlying mechanisms, and the second issue limits the ability of machine learning algorithms to accurately deduce the dynamics of the disease. To address these challenges and achieve a more accurate output, we initially trained an inverse method network using a synthetic dataset. Subsequently, we utilized patient-specific MRI data as input to derive key modelable parameters, including tumor growth and infiltration rate, tailored for each patient. These parameters are then integrated into our mathematical models to enhance their precision and relevance. Furthermore, we incorporated clinical and radiomics data to enhance the non-modelable component of our approach, which involves the application of machine learning methods. In the end, we develop a Bayesian combination of mechanistic modeling and machine learning algorithms to increase the accuracy of our patient-specific predictions. This approach allows us to see the probability distribution of time to recurrence for each patient and can be beneficial to optimize the second line of treatment for each patient.

ECO-EVOLUTIONARY MODELS FOR TRAIT EVOLUTION AND MINIMUM VIABLE POPULATION SIZES IN A CHANGING ENVIRONMENT

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Human-induced environmental changes are believed to be the current major threat to biodiversity. It is thus critical to understand better the conditions under which populations can successfully adapt and persist in a changing environment. Classical models predict that populations track the changing environment and asymptotically establish an equilibrium lag, allowing population persistence as long as the rate of environmental change does not exceed some critical rate. However, it is unclear how large populations must be to persist, i.e., minimum viable population (MVP) size for adaptation in a changing environment. In addition, it is crucial to understand how long it takes populations to build a sufficient adaptive response from the onset of environmental change and how this duration depends on population parameters. Using individual-based modelling and mathematical approximations based on Taylor expansion and Chebyshev polynomials, we model the evolution of a quantitative trait determined by a finite number of di-allelic loci that determines an individual fitness. Unlike in most previous models, our models allow changes in trait variance due to selection, genetic drift, and mutation. Our models also account for non-linear relationships between fitness and trait variation. We found that MVP size decreased with increasing mutation rates but was not influenced by initial trait variation. Populations also fall into three main categories depending on how they respond to the deteriorating environment, i.e., those that (a) went extinct before attaining an equilibrium lag, (b) went extinct after attaining an equilibrium lag, and (c) persisted after attaining an equilibrium lag. The equilibrium lag was established faster in larger populations with higher mutation rates but slower in populations with larger standing genetic variation. We recommend measures that increase population size, habitat carrying capacity, and inflow of new variation.

EPIDEMIOLOGICAL IMPLICATIONS OF SYMPTOM PROPAGATION IN RESPIRATORY PATHOGENS

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Symptom propagation occurs when the symptom set an individual experiences is correlated with the symptom set of the individual who infected them. Symptom propagation may dramatically affect epidemiological outcomes, potentially causing clusters of severe disease. Conversely, it could result in chains of mild infection, generating widespread immunity with minimal cost to public health.

To understand the present state of the epidemiological and biological evidence for the propagation of symptom severity for a broad range of pathogens of public health concern, we initially detail our findings from a scoping review of 14 respiratory pathogens. We summarise the accumulating evidence that symptom propagation occurs for many respiratory pathogens.

Furthermore, the mechanistic representation of symptom propagation within mathematical modelling of respiratory diseases is understudied. We present a novel compartmental, ordinary differential equation model structure for incorporating different strengths of symptom propagation into models of infectious disease transmission via a single parameter, alpha. Varying alpha tunes the model from having no symptom propagation (alpha=0, as typically assumed) to one where symptoms always propagate (alpha=1).

Implementing the model in the case where symptoms are either mild or severe, we show that the strength of symptom propagation has profound effects on infectious disease outbreaks, including notably on the proportion of cases that are severe. Using the model to simulate the control of influenza and SARS-CoV-2 using vaccines of two types (infection-blocking and symptom-attenuating), we demonstrate that vaccines that reduce symptom severity are more effective in reducing severe and overall cases under the assumption of stronger symptom propagation. We also show that knowing the strength of symptom propagation can help understand the relative effectiveness of these two types of vaccines, helping to shape disease control strategies.

MODELLING OF LEPROSY AND EFFECT OF AWARENESS PROGRAMS DURING DISEASE TRANSMISSION: A CONTROL BASED MATHEMATICAL APPROACH

Priti Kumar Roy (Jadavpur University)
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Among all historically known diseases, leprosy is the most complicated and neglected one and among all the persistent challenges in leprosy eradication goals, illiteracy, ignorance and lack of social awareness are the most crucial factors need to be tackled. In this connection, to develop a realistic mathematical model, two key points are being specifically focused in our study. The first one takes into account the social challenges, awkwardness faced by the affected persons and the ignorance which eventually develops the most-feared pathway of late diagnosis. The other one is evaluating proper control therapeutic strategies by invoking social awareness via mass media campaign and making the susceptible, asymptomatic and symptomatic unaware people able to gather substantial amount of knowledge about leprosy to implement in the daily life scenario. Our seven dimensional nonlinear ODE-based model constructed to tackle the above mentioned vital issues, is investigated for existence of solutions, boundedness, positive invariance and different stability examinations and then, an optimal control-induced system is formulated and analyzed by incorporating two time dependent control measures. Using Pontryagin's minimum principle, suitable optimal control profiles are evaluated and rational optimistic guidelines are presented for the eradication of leprosy in near future. All of our analytical results are verified through numerical simulations in Matlab2016 and are compared with real clinical data from some recent experimental studies.

IMPROVING DRUG DELIVERY IN THE BRAIN USING MICROBUBBLES COMBINED WITH FOCUSED ULTRASOUND

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The brain-blood barrier (BBB) is the major barrier protecting the brain, which consists of endothelial cells that are connected by tight junctions between the neighboring cells. This BBB limits the transport of drugs from the blood into the brain. To increase the permeability of the BBB and hence drug delivery into the brain, applying a combination of microbubbles (MBs) and focused ultrasound (FUS) shows a great potential. In this process, the MBs start to oscillate due to the FUS and "massage" the membrane of endothelial cells resulting in small, temporary openings in the endothelial cell membrane and in between the cells.

To describe the oscillations of the MB resulting from the driving acoustic pressure of FUS, the Rayleigh-Plesset equation is used [1]. In our approach, we also take into account the movement of the MBs, combined with the FUS. For that, we no longer assume that the MB is a sphere or a circle in two-dimensional case: the membrane of MB is splitted into many line segments connected by the nodal points. Subsequently, the displacement of every nodal point on the membrane is precisely tracked. The displacement of the nodal point is determined by multiple processes. When a MB is very close to or collides the endothelial cells, shear stress on the endothelial cells is produced which has a significant impact on increasing the permeability of the BBB.

In this presentation, we present a model that describes the evolution of the geometry of migrating MBs and we compare our results with the model that takes MBs as spherical objects. Our model and results provide a next step towards understanding the influence of MBs combined with FUS on the permeability of the BBB.

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THE SHAPE OF SLEEP: HOW TIMESCALE SEPARATION REVEALS GEOMETRIC STRUCTURE IN A MATHEMATICAL MODEL OF THE SLEEP/WAKE CYCLE

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We are estimated to spend one third of our life asleep, and it is increasingly apparent that good sleep is essential for overall health. Yet many people suffer from insufficient sleep or sleep disorders. Even though we do not fully understand why we sleep, mathematical models do exist that capture the broad features of sleep-wake regulation and are widely used in safety-critical industries to model fatigue risk. Most mathematical models do not consider the fact that during the night we cycle between two main sleep states (rapid eye movement (REM) and non-rapid eye movement (NREM) sleep). An exception is the Behn-Booth model which consists of an 8-dimensional system of differential equations that captures the firing of the neuronal groups that control wake and sleep states. The model further incorporates more global aspects of sleep regulation, including a use-dependent homeostatic drive and the action of the daily circadian body 'clock'. The Behn-Booth model has been analysed as a two-timescale fast-slow system and as a discontinuous circle map. These approaches have provided useful insight into the mechanisms by which different sleep patterns can be produced. Here, we show that the Behn-Booth model may usefully be considered as a three-timescale problem. We show that this three-timescale decomposition reveals additional geometric structure which acts to organise oscillations between REM and NREM states. The additional structure enables us to understand the model factors determining the duration of REM-NREM cycles and the relative time spent in each state. The three-timescale setting also shows how different numbers of REM-NREM cycles lead to discontinuities in the circle map description. This deeper geometric understanding of the generation of REM-NREM cycles brings insight into the relationship between model predicted and observed patterns of REM-NREM cycles and suggests ways in which models could be modified to more accurately reflect patterns of human sleep.

STRATIFYING AND PREDICTING THE PROGRESSION OF ACUTE LIVER FAILURE DURING THE EARLY PHASES

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Acute liver failure (ALF) stands out as one of the most severe diseases, marked by rapid pathological changes that often lead to multi-organ failure and, ultimately, death. Currently, effective treatment strategies, aside from transplantation, remain elusive. Furthermore, there is a lack of a quantitative indicator to predict which patients hospitalized with acute liver injury (ALI) will develop severe conditions, such as the need for liver transplantation, despite significant variations in disease progression. In our study, we analyzed data from 320 patients admitted to the hospital with ALI. Employing a machine-learning approach to time-course blood test data and assessing Shapley additive exPlanations (SHAP) algorithm, we identified prothrombin time (PT) as a biomarker reflecting individual ALF conditions. We stratified ALF progression into six patterns, each indicating different levels of severity based on PT dynamics. Notably, these patterns were well predicted by clinical datasets at the time of admission. Additionally, utilizing mathematical modeling and machine learning, we assessed the predictability of individual PT dynamics during the early phase of acute liver injury

MATHEMATICAL MODELLING OF MITOCHONDRIAL FUNCTION: ANALYZING THE CELLULAR ATP LANDSCAPE.

Rajneesh Kumar (University of Bergen, Norway)
Other authors: Iain G. Johnston

Adenosine triphosphate (ATP) is a universal "energy currency" in biology, used to power processes from movement to thought. To satisfy the cell's energy requirements, ATP must be produced and distributed to where it is needed. Mitochondria, vital cellular organelles, dominate the production of ATP in most cells in complex organisms. However, the spatial and temporal distribution of ATP within the cell, and how this landscape is shaped by the complex and dynamic arrangement of mitochondria in the cell, remains largely unknown. This intricate, but poorly understood, relationship between mitochondrial function and the cellular ATP landscape is of pivotal importance for numerous subcellular processes, dysfunction in which causes devastating diseases.

In response to this gap in understanding, we are working with a mathematical model using reaction-diffusion equations to describe the time-varying spatial distribution of ATP within a cellular environment, with a specific focus on incorporating dynamic mitochondria as sources. We delve into the mystery of mitochondrial structure variation, exploring why some cells maintaining fragmented mitochondria while others exhibit fused structures.

A peculiar ongoing debate revolves around the existence of ATP gradients within the cell. Despite compelling quantitative arguments supporting the spatial variation of ATP concentration, it is sometimes argued that rapid diffusion negates the possibility of concentration gradients. Our project refutes this perspective, providing modelling arguments supported by quantitative analysis.

In essence, our work establishes a foundation for understanding the complex interactions between mitochondrial function and the cellular ATP landscape. The resulting mathematical model offers a tool for simulating the effects of changes in mitochondrial dynamics on ATP distribution.

MULTIDOMAIN MODELS FOR IONIC ELECTRO-DIFFUSION IN BIOLOGICAL TISSUES

Raúl Felipe Sosa (Faculty of Sciences in Physics and Mathematics, Autonomous University of Chiapas)

In this presentation, we will discuss multidomain models for ionic electro-diffusion in biological tissues. These models, originally proposed by Yoichiro Mori in 2015, form a class that facilitates the modeling of pathologies in various organs, such as the brain and the heart. Mathematically, these models are fully nonlinear, coupling parabolic and elliptical partial differential equations (PDEs) with ordinary differential equations (ODEs), presenting a profound mathematical challenge.

Throughout the presentation, we will briefly introduce two application examples: the bidomain model, which models the electrical activity of the heart, and a model describing the channeling and diffusion of calcium in biological tissues. We will present recent results, with a focus on the well-posed formulation of boundary problems and the characterization of the phase space for these intricate models.

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SCALABLE MACHINE LEARNING METHODS TO DETECT MEANINGFUL LINEAGES IN VIRAL POPULATIONS FROM LARGE AMOUNTS OF GENETIC DATA

Roberto Cahuantzi (University of Manchester)
Other authors: K. Lythgoe, L. Pellis, I. Hall, T. House

The advent of the new genetic sequencing technologies and the renewed interest on pandemic prevention generate the imperative to devise methods that can cope with millions of sequences to retrieve crucial information from this wealth of data. Novel Machine Learning tools allow us to gain insights into the genetic landscape of a viral population in highly efficient way and minimising the need for manual curation.

We analysed approximately 5.7 million SARS-CoV-2 genetic sequences applying k-mer word-statistics characterisation, state-of-the-art PaCMAP dimensionality reduction, CLASSIX clustering and Gaussian Process regression smoothing techniques to gain insight into the genetic landscape and evolutionary dynamics of the viral population. Our proof-of-concept approach explores methods to produce computationally efficient and automatic analyses that have the capability to handle many orders of magnitude more sequences than current "gold standard" phylogenetic methods.

The proposed method relies on an approximation of the genetic similarities among viruses to detect growing or shrinking trends of clusters of similar viruses likely to belong to the same sublineage. Its computational efficiency then gives it the potential to produce "snapshots" of the genetic landscape of a viral population without the need to subsample the available data at the time and place of interests, which makes it less prone to blind spots and delay detection of a growing lineage. Refinements of this method could improve the early detection of variants of concern at any given time without relying on human curation.

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LESSONS LEARNED FROM EPIDEMIC MODELING FOR COVID-19 WITH REAL-WORLD DATA

Roberto Kraenkel (São Paulo State University/ IFT-UNESP/ São Paulo, Brazil)

In this presentation we discuss mathematical models for Covid-19 epidemics through an example of a model for an outbreak due to a new variant (Gamma-variant), in the Amazonian region, Brazil. We propose a model adapted to the available data and show its usefulness by estimating transmissibility and reinfection of the then novel variant.

The model used is an age-structured SEIR-like model, with the infectious compartment divided in Asymptomatic, Hospitalized and Infected-but-not-hospitalized compartments. Data used comes from micro-data for the weekly incidence and the proportion of cases due to the new variant.

Besides showing that the high infectiousness of the novel variant our results pointed out that only with a certain level of reinfections (28% of the cases) the situation in the city of Manaus could be understood, a result later validated by field work.

This presentation highlights the use of models for estimating basic characteristics of an epidemic (transmissibility) and testing hypothesis about mechanisms driving an outbreak (re-infections).

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STOCHASTIC MODELLING REVEALS COMBINED REGULATION STRATEGIES MAINTAINING HOMEOSTASIS IN STEM CELL POPULATIONS

Rodrigo García-Tejera (University of Edinburgh)
Other authors: M. Amoyel, R. Grima, L. Schumacher.

To maintain and regenerate adult tissues after injury, the numbers, proliferation, and differentiation rates of tissue-resident stem cells must be precisely regulated. The regulatory strategies, whether there is coordination of different mechanisms, and how to detect them from snapshots of the populations, remains unresolved. Recent findings in the Drosophila testes show that commitment to differentiation is actively regulated. Prior to differentiation, somatic stem cells transition to a state that license them to differentiate upon receiving a commitment signal, but remain capable of fully regaining stem cell function. For proper tissue function, the coordination between the differentiation of somatic and germline stem cells is crucial, making it critical to understand how regulation prevents exhaustion or overgrowth of both populations. Here, we build stochastic models for the Drosophila testes to investigate how licensing contributes to homeostasis, recovery after injury and the regulation of the variability of stem cell numbers. We find that regulation through licensed states is efficient at maintaining a stable homeostatic state and preventing stem cell extinction. Experimental data argues for the likely presence of regulation through competition for niche access. Competition for niche access contributes to the reduction of the variability of stem cell numbers but does not prevent extinction. Our results suggest that a combination of both regulation strategies is needed to reduce variability and prevent extinction simultaneously.

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HYDRODINAMIC LIMITS FOR MODELING ANOMALOUS IMMUNE RESPONSE: A FOCUS ON MULTIPLE SCLEROSIS

Romina Travaglini (Istituto Nazionale di Alta Matematica)

We present the latest results in studies modeling anomalous immune responses, which extend the work proposed in the literature. These models describe the dynamics over time of a large number of interacting cells within an autoimmune framework, utilizing the tools of the kinetic theory of active particles. We describe a spatio-temporal model, considering the motion of immune cells stimulated by cytokines and applying it to a specific autoimmune disease, Multiple Sclerosis. We derive macroscopic reaction- diffusion equations for the number densities of the constituents with a chemotaxis term. A natural progression is to study the system, exploring the formation of spatial patterns through a Turing instability analysis of the problem, and basing the discussion on microscopic parameters of the model. In particular, we observe spatial patterns that reproduce the brain lesions characteristic of the pathology during its different stages. We also propose a weakly nonlinear analysis of the model to study the stability of patterns in two dimensions. Finally, the study of analogous systems is performed including treatment terms.

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NOTCH FLOW-DRIVEN POLARISATION AND SIGNALLING IN VESSELS - A MATHEMATICAL MODEL

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During sprouting angiogenesis, new blood vessels grow from existing ones. This process plays a crucial role in organ development and repair, in wound healing and in numerous pathological processes such as cancer progression or diabetes. In sprouting angiogenesis, endothelial cells degrade the matrix, proliferate and move in concerted manner, following mechanical and chemical cues. The Notch signalling pathway, involving Delta-4 and Jagged-1 ligands, determines tip cell selection and vessel branching. Recently it was shown that, in a functional vessel, the Notch membrane protein accumulates at the back of the cell, opposite to the flow direction. To explore the consequences for tip cell selection of this Notch polarisation, we built a 3D multi-phase-field model of the endothelial cells in a vessel that takes into account the lumen, the extracellular matrix, endothelial cells' elongation in the direction of the flow, and cell rearrangement. Using this model, we observe how lateral inhibition in a vessel is dependent on the Notch, Delta and Jagged ligands localisation within the endothelial cells. Moreover, we predict how Notch polarisation affects the observed positioning of Delta-rich cells in vessels of different diameters and in cell cultures under flow.

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A FLUX BALANCE ANALYSIS MODEL FOR THE AMMONIA-OXIDIZING ARCHAEON N. VIENNENSIS

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Ammonia-oxidizing archaea play a crucial role in the nitrification step of the nitrogen cycle, in which they oxidize ammonia into nitrite, a precursor to nitrous oxide. Consequently, they significantly contribute to the ever-increasing levels of nitrous oxide on our planet [1]. In light of the detrimental impact nitrous oxide emissions have on our environment, it is of great importance to study how exactly the metabolism of ammonia-oxidizing archaea responds to changes in the concentration of available nutrients or nitrification inhibitors. Nitrososphaera viennensis, a prevalent soil ammonia-oxidizing archaeon, has now emerged as a model organism [2]. A metabolic network model for it can shed light on the intricate mechanisms of its biochemical pathways.

We present a genome-scale model emulating the metabolism of Nitrososphaera viennensis. The 635 reactions in the model encapsulate its core metabolism, as well as several secondary pathways. To construct this model, we used the flux balance analysis method [3], a mathematical approach seeking an optimal set of reaction fluxes for the model and operating on two key assumptions: a) the reaction fluxes are subject to the steady-state condition: the concentrations of the metabolites do not change over time, and b) the nutrient uptake fluxes are constrained based on experimental data. These assumptions result in a finite solution space, encompassing all potential flux distributions. Linear programming is then utilized to identify an optimal solution within this space, which is the primary outcome of a flux balance analysis model.

This model can guide further exploration of the metabolism of Nitrososphaera viennensis, offering insights also applicable to ammonia-oxidizing archaea in general. Specifically, the comparison of fluxes predicted in different environments for a reaction involved in nitrite production can open new avenues for potential strategies to minimize the organism's nitrite production.

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SENSING ELECTRICAL ENVIRONMENTS: THE UNIQUE SENSE OF ELECTRORECEPTION

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Recently, bees and spiders (and other such arthropods) have been shown to detect electrical fields (a sense known as electroreception). Whilst this novel discovery expands our view of how such organisms explore their environment, exactly how this curious sense works remains unclear. With such new discoveries, many questions arise that require both theoretical and empirical examination. In this talk, I will introduce the fundamentals of this sensory phenomena, and uncover some of the mechanical and sensory complexities that have been discovered through mathematical studies.

I will explain the mechanics of electroreception via sensory hairs and show the physical and biological feasibility of this sense. From this basis, I will delve deeper into the interactions between hairs and electrical fields introducing the concept of a sensitivity contour (regions of the solution space where hairs deflect to a given sensory threshold), and examine how a hair's sensory capability changes owing to electrical interactions between hairs. Finally, I will discuss some of the sensory possibilities of electroreception (e.g. object identification and location detection) and the biological implications of this (e.g. foraging decisions, predator-prey behaviour).

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ANALYSIS OF EFFECTS OF INTERREGIONAL AND INTERNATIONAL MIGRATION ON JAPAN'S POPULATION DECLINE USING A MULTI-REGIONAL LESLIE MATRIX MODEL

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According to the census, Japan's population has declined for the past decade since 2010. The reason is the birth rate, which has been below the population replacement level since 1975, and the total fertility rate in Japan in 2022 is 1.26, the lowest level ever. Among the 47 prefectures in Japan, Tokyo has the lowest fertility rate at 1.04. Conversely, Okinawa has the highest total fertility rate at 1.70. Excluding the coronavirus disaster, the percentage of foreign residents in Japan is increasing, and it is estimated that 10% of the total population will be foreigners by 2070. Therefore, in this study, we analyze the effects of regional fertility rates, interregional migration, and immigration on population growth rates by sensitivity analysis using a multiregional Leslie matrix model. Our analysis shows that migration from urban areas and immigration to regions with high reproductive value contribute to mitigating population decline.

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COMPARISON OF ACCOMMODATION RESERVATION AND MOBILE PHONE DATA TO UNDERSTAND BEHAVIORAL RESPONSE AGAINST EMERGING INFECTIOUS DISEASE OUTBREAK

Ryosuke Omori (Hokkaido University)
Other authors: Koichi Ito

Forecasting the behavioral response against emerging infectious disease is important to forecast the future course of emerging infectious diseases dynamics. To forecast human behavioral change in response to the change of epidemic situation, understanding the dynamics of human behavioral change is required. However, the decision-making of behavioral response against the infectious disease is difficult to estimate due to the availability of data. In response to this, we have proposed the use of accommodation reservation data [1] and discovered the laws in the behavioral response to the emerging infectious disease outbreak [2]. The accommodation reservation data can capture only the relatively long-scale movement and it may not be possible to capture the general trend of behavioral change against infectious disease outbreak. To assess this, we compared the accommodation reservation data with the human movement data recorded in the mobile phone location data. We constructed the model describing the relation between accommodation reservation and mobile phone location data to assess the generality of accommodation reservation as the measurement of behavioral response to infectious disease outbreak. Also, we analyzed when humans decide their future behaviours decision-making against outbreaks of infectious diseases using our developed model.

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A DIFFERENTIAL GEOMETRIC ANALYSIS OF PERPETUAL AND EQUILIBRIUM POINTS IN MULTISTABLE DYNAMICAL SYSTEMS

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Perpetual points (PPs) are critical points in dynamical systems where the acceleration becomes zero while the velocity remains non-zero. They have been observed in both continuous-time and discrete-time systems, and have been shown to be useful for tracing stable fixed points, identifying unexpected attractors, and localizing co-existing attractors.

In this talk, I shall introduce an analytical framework for understanding the distribution and characteristics of perpetual and equilibrium points within the phase space of multistable biological systems. I shall present theoretical conditions for the existence, and bounds on the number of PPs in the phase space. The talk will highlight the relevance of our results in understanding the dynamics of complex, multistable biological systems.

MEASURING THE SIMILARITY BETWEEN SINGLE-MOLECULE LOCALISATION MICROSCOPY DATASETS: A DATA-DRIVEN MACHINE-LEARNING APPROACH

Sandeep Shirgill (University of Birmingham)

Single-molecule localisation microscopy (SMLM) is a member of a family of "super-resolution" fluorescence microscopy methods that break the traditional resolution limit of optical imaging, allowing researchers to access nanoscale spatial scales.

The data from SMLM is not in the form of traditional microscopy images (i.e. arrays of pixels), instead, SMLM data is pointillist – a list of the xyz coordinates of labelled molecules, where each dataset consists of multiple regions of interest (ROIs). From these ROIs, protein nanoscale organisations, can be observed in cells. Currently, there is no published method that characterises spatial organisation of proteins in a cell and how this can vary between different cells or within the same cell under different conditions (e.g. before and after drug treatment).

Here, a machine-learning approach is utilised to embed SMLM ROIs in a two-dimensional latent space, from which, other similar ROIs can be identified. Firstly, ROIs are passed through a contrastive-learning neural network which has been trained to recognise biologically-relevant differences (e.g. cluster sizes) but ignore irrelevant difference (e.g. rotations of the ROI). The neural net will then output these ROIs into a high-dimensional embedded space where distance between ROIs in this space is proportional to how similar ROIs are (e.g. two ROIs that show statistically similar character will be closer together). The dimensionality reduction technique, Uniform Manifold Approximation and Projection (UMAP) [1] is then used to reduce the dimensions of the latent space to 2D for better visualisation of the data in latent space.

Using this technique, the diversity that exists for nanoscale organisational similarity between cells, proteins, species etc. could be revealed. This would provide the first information on the diversity of nanoscale organisation.

OPTIMAL CONTROL IN THE PRESENCE OF PARAMETRIC UNCERTAINTY: A CASE STUDY IN EPIDEMIOLOGY

Sandra Díaz-Seoane (Non-linear Control Group, Department of Engineering Systems and Automation, Universidade de Vigo)
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We present a study on the application of optimal control theory to epidemiological models, specifically focusing on the issue of parametric uncertainty. Optimal control is a branch of control theory that deals with finding an input to a dynamical system over a period of time such that an objective function is optimized. It has numerous applications in science and engineering. Parametric uncertainty arises from model parameters whose exact values are unknown, and cannot be estimated precisely by statistical methods. This uncertainty can significantly impact the predictability and control of complex systems. We use as a case study the susceptible–infected–removed model with confinement and deaths presented in [1], the structural identifiability of which was analysed in [2]. The time at which the growth in the number of infected individuals halts and starts decreasing cannot be calculated with certainty before the turning point is actually attained [1]. This inherent unpredictability in the progression of an epidemic, akin to parametric uncertainty, poses significant challenges to the application of optimal control. Here we explore these challenges and propose methodologies for the application of optimal control in epidemiological models in the presence of parametric uncertainty. Our findings highlight the importance of considering parametric uncertainty in the design of control strategies for managing the spread of diseases.

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MODELLING DIFFERENTIAL ADHESION IN STOCHASTIC AND MEAN-FIELD MODELS OF CELL MIGRATION

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Cell-cell adhesion plays an important role in many biological processes such as tissue formation and maintenance, wound healing and cancer metastasis. From a mathematical perspective, differential adhesion has been studied using stochastic discrete and continuum models based on partial differential equations (PDEs) and it is frequently desirable to link the former to the latter as both modelling paradigms have their use in different biological/experimental scenarios. For example, one may opt for a discrete model when the behaviour of each individual cell is of interest. However, when scaling up from single cells to tissue level, continuum models may be more desirable because individually modelling each cell in a large population can be computationally prohibitively expensive.

In this talk, I will outline the development of an on-lattice agent-based model (ABM) for cell migration with cell-cell adhesion and swapping in a population consisting of two cell types. I will derive the corresponding continuum model and demonstrate that while the continuum model works well for some parameter ranges, it fails to represent the true dynamics of the ABM in others. Specifically, biological cell patterning such as aggregation and segregation are inaccessible in the continuum model. Instead, I propose a set of stochastic mean equations which better capture the full range of behaviours of the ABM in one and two dimensions.

LEVET SET METHOD FOR PLANT WITH GROWING LESIONS

Sheila Rae Permanes (Université de Picardie Jules Verne)
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Plant-disease phenotyping is crucial for plant pathologists in the assessment of host- resistance and pathogen aggressiveness. It provides better understanding on pathogen spread within hosts, pathogen evolution and control, and plant breeding for pathogen resistance. Phenotyping is usually performed from visual scoring to image segmentation. In this study, we combine image-based phenotyping with mathematical modeling to improve plant disease quantification by analyzing the spatiotemporal dynamics of plant-pathogen interactions when the pathogen causes growing lesions on plant tissues. This study utilized a readily available set of images of the spread of Peyronellaeapinodes on the stipules of two pea cultivars that were monitored daily with visible imaging. We implemented a level-set method to describe the dynamic deformation of the leaf and the lesion growth. Boundaries of the lesions are less sharp and less smooth as appearing in the pixel-segmented images and it makes difficult to detect. Hence, the marching squares was applied to extract the contour of the lesions, and transformed them into binary images before implementing the level-set method. The signed distance is computed from daily images of lesion and leaf. We will present how good the mathematical model is to capture and track the evolution of the leaf deformation and lesion growth of the two pea cultivars through visual representations and metric measures. This comparison can be a critical step in this newly established ap- proach of plant disease phenotyping since it ascertains the method's accuracy and reliability for the mathematical algorithms and techniques used in disease detection and segmentation, supports research validity, and can also contribute to the practical implications for biology, agriculture and similar fields.

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QUANTITATIVE EVALUATION OF BYPASS PATHWAYS ON THE DIFFERENTIATION POTENTIAL OF HEMATOPOIETIC STEM CELLS

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Hematopoietic stem cells (HSCs) are the cell population responsible for blood cell production. Understanding the differentiation potential and long-term productive capacity of HSCs will contribute to understanding the causes of hematopoietic-related diseases and establishing treatments for them. The functional capacity of HSCs is evaluated by transplantation assays in mice and other animals. Observations in this experiment include the ability of the transplanted cells as well as the results of competition in proliferation with competitor cells that are transplanted at the same time. We analyzed cell frequency measurements of three myeloid lineages and one lymphoid lineage in an experiment in which single-HSC was transplanted. We developed a mathematical model in which long-term HSCs (LT-HSCs) differentiate into progenitor cells of each lineage through short-term HSCs (ST-HSCs), and mature cells are produced. Based on previous findings, we hypothesized the existence of a bypass pathway in which LT-HSCs produce myeloid lineage progenitors without going through ST-HSCs. Using a nonlinear mixed-effects model, we estimated the parameters of the mathematical model for individual transplantation data. The estimated dependency of the myeloid bypass pathway was high for the platelet lineage and close to zero for the neutrophil/monocyte and erythroid lineages. True LT-HSC, assessed by their ability to produce blood cells in a secondary transplantation, were found to maintain a high dependency on the platelet bypass pathway throughout the entire transplantation period. We also found that HSCs transplanted from aged donor mice consistently had a higher dependency on the pathway (50%) at the end of the transplantation. These results suggest that the platelet bypass pathway is required to maintain long-term blood cell production capacity and that the age-related bias toward platelet production is due to an increased degree of dependence on the bypass pathway.

HIGH-ORDER NUMERICAL MODEL FOR THE LIGHT PROPAGATION IN THE CORNEA

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The class of discontinuous Galerkin (DG) methods are renowned for their effective resolution of PDEs within intricate geometries. However, these methods necessitate the mesh to align with the geometry. Preserving the optimal convergence order of DG discretisations in curved domains and curved interfaces is a critical and well-known issue. Such problems arise naturally when modelling biological tissues. Motivated by the corneal opacity problem, we will present the discontinuous Galerkin (DG) method combined with a polynomial reconstruction method (DG–ROD method) as an efficient strategy that does not rely on curved meshes nor compromise the stability and convergence properties of the numerical method.

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CAN SMOKING ALTER PSYCHOLOGY?

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The gut-brain axis is the bidirectional communication between the gut and the brain associated by different pathways involving the nervous system, the metabolic system, body's microbiota, and the immune system. It is known that smoking has an impact on the oral microbiota. We hypothesize that via the gut-brain-immune axis changes can be conferred in the brain function and eventually in human psychology. We employ the oral microbiota data which intends to understand aspects of the gut-brain-axis problem, especially for heavy-smoker population. There are three variables with several features as follows: Psychological traits has 5 features (Extraversion, Agreeableness, Conscientiousness, Negative Emotionality, and Open Mindedness); Metabolic Pathways has 46 metabolic pathways; and Bacteria Composition has 78 genera. A total of 105 samples were drawn from the UAE residents. We employ canonical correlation analysis to reduce the dimensions of the three datasets into 3 scalar coarse variables representative for bacteria composition, metabolic function, and psychological profile. Our analysis allows for identifying the most important features that contribute to our coarse variables. Subsequently, a nonlinear regression allows to see how these variables interact with each other. Then we assume that the expected value of the healthy population data represents a stable steady state of the system. Thus, our regression system can be considered as the steady state response of the potential system dynamics. Then, using linear stability analysis we can identify the stability properties of the system. The results stated that there is a strong association between the metabolic pathway and bacteria composition. Besides, there is a direct linear influence of metabolic pathways to the psychological trait for non-smoker. However, this is not the case for the smoker. We also have a stable point from the system where the values are close to the mean value of the scaled data for non-smoker

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MODELLING IL-2 SIGNALLING DYNAMICS FOR A SINGLE T CELL

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Interleukin-2 (IL-2) is a cytokine which can both promote and suppress immunity by binding to effector and regulatory T cells respectively [1]. The seemingly contradictory effects of IL-2 have raised interest in selectively stimulating the effector or the regulatory T cells to promote or suppress immunity by generating different formulations of IL-2 that preferentially stimulate certain types of T cells. For the rational development of a range of immune-modulatory therapeutics, it is important to understand the role of IL-2 in mediating interactions between different types of T cells. We start by modelling the dynamics of IL-2 binding to T-cell receptors on the individual cell scale. Our objectives are to determine whether spatial effects, including distribution of IL-2 in the bulk and 2D surface diffusion on the cell membrane, are important, to investigate model misspecification between the spatial and the non-spatial models and to determine when and how we can approximate the physiological spatial PDE model using a simple ODE model. We want to examine whether non-spatial models can accommodate spatial effects. Thus, we have developed and studied spatial PDE and non-spatial ODE models to examine the most relevant features, for example spatial geometry, availability of IL-2 and its receptor and binding kinetics, for absolute and relative levels of bound IL-2 receptors. To analyse and compare the models, we have used various techniques including model reduction, steady state analysis, numerical simulation, global parameter sensitivity analysis, structural and practical identifiability. We will present results obtained in these studies and discuss their impact.

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MODELLING AND SIMULATION OF INTRACELLULAR SIGNALLING PATHWAYS: COUPLING CHEMICAL PROCESSES AND MECHANICAL PROPERTIES

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Communication and interactions between cells happen mostly through intercellular signalling processes. These signalling pathways are important in all physiological activities of the cell, such as cell division, cell movement, immune response, and tissue development. In many of these signalling pathways, the chemical processes and mechanics of the cell work together [1]. However, how exactly these two phenomena communicate is not well known. A common way to model the chemical processes of cell signalling pathways are reaction-diffusion equations [2]. The mechanical properties of the cell are modelled assuming elastic constitutive relationships. Regarding the chemical process, our model includes the diffusion of signalling molecules and membrane receptors, and the reactions between the molecules and receptors. This is coupled to the mechanical properties such that the mechanics of the extracellular matrix influences the interaction between the signalling molecules and the results of the signalling pathways affect the deformation of the cell. To explore this coupling, we model the cell signalling processes involving the Rho signalling molecule, which is known to interact with the mechanical properties of the cell and the extracellular matrix [3]. Simulation results, benchmarking and a comparison to experimental observations will also be presented.

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MODELLING THE REGULATION OF CHRONIC WOUNDS BY TISSUE INHIBITORS OF MATRIX METALLOPROTEINASES

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Understanding the biochemistry and pharmacology that underpins chronic wounds and wound healing is of high importance as there are over 2 million people in the UK suffering from chronic wounds. Chronic wounds are susceptible to high levels of Matrix Metalloproteinases (MMPs), which are responsible for the modification and proliferation of healthy tissue. High concentrations of MMPs however cease to be beneficial and can lead to the destruction of the healthy tissue. Tissue inhibitors of MMPs (TIMPs) are produced in response to MMPs and are responsible for the regulation of MMP concentrations and thus the development of chronic wounds. In this talk, we propose a mathematical model that focuses on the interaction of dermal cells, MMPs and TIMPs in the healing process using a system of partial differential equations. Using a parameter set corresponding to healthy biological functioning, we observe the emergence of travelling waves corresponding to a front of healthy cells invading a wound. From the arising travelling wave analysis, we observe that deregulated apoptosis results in the emergence of chronic wounds characterised by a hysteresis effect when apoptotic rates are varied. We observe that this hysteresis effect disappears when TIMP production is increased, providing insights into the role of TIMPs as a regulator of healing. In extending our wound to a two-dimensional spatial domain, an influx of TIMPs to a chronic wound by means of a Robin boundary condition results in the complete healing of a chronic wound, providing further insight into the management of chronic wounds.

COALESCENTS WITH MIGRATION IN THE MODERATE REGIME

Sophia-Marie Mellis (Bielefeld University)
Other authors: F. Cordero, S. Hummel, E. Schertzer

Multi-type models have recently experienced renewed interest in the stochastic modeling of evolution. This is partially due to their mathematical analysis often being more challenging than their single-type counterparts; an example of this is the site-frequency spectrum of a colony-based population with moderate migration.

In this talk, we model the genealogy of such a population via a multi-type coalescent starting with N(K) colored singletons with d greater than 1 possible colors (colonies). The process is described by a continuous-time Markov chain with values on the colored partitions of the colored integers in 1,..., N(K); blocks of the same color coalesce at rate 1, while they are also allowed to change color at a rate proportional to K (migration).

Given this setting, we study the asymptotic behavior, as K goes to infinity at small times, of the vector of empirical measures, whose i-th component keeps track of the blocks of color i at time t and the initial coloring of the integers composing each of these blocks. We show that, in the proper time-space scaling, it converges to a multi-type branching process (case N(K) approx. K) or a multi-type Feller diffusion (case N(K) greater than K). Using this result, we derive an applicable representation of the site-frequency spectrum.

This is joint work with Fernando Cordero, Sebastian Hummel and Emmanuel Schertzer.

MATHEMATICAL MODEL OF CAR-T-CELL THERAPY FOR A B-CELL LYMPHOMA LYMPH NODE

Soukaina Sabir (MOLAB-University of Castilla-La Mancha)
Other authors: O. León-Triana, S. Serrano, R. Barrio, Victor M. Pérez-García.

CAR-T cell therapies have demonstrated remarkable success in treating B-cell leukemia among children and young adults. However, their efficacy encounters hurdles when addressing B-cell lymphomas, characterized by solid masses in lymph nodes, glands, or organs. This contribution unveils a mathematical model specifically designed to analyze the interplay between diffuse large B-cell lymphoma and CAR-T cells within the microenvironment of a lymph node. The mathematical model serves as a robust tool for unraveling dynamic complexities among cell populations, providing insights into unique causes of treatment failure specific to B-cell lymphomas. A particular focus is placed on understanding immunosuppression induced by tumor cells and its consequential impact on the dynamics of cellular interactions within the lymph node. Through the exploration of diverse response scenarios, we highlight the pivotal role of product characteristics in determining treatment outcomes. This research enhances our understanding of inherent challenges in CAR-T cell therapies for B-cell lymphomas, offering valuable insights that guide the development of refined strategies to overcome treatment obstacles.

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OPTIMIZING RESOURCE ALLOCATION TO DEFENCE CHEMICALS AND COUNTER-COUNTER DEFENCE BY ENZYME INHIBITORS IN PARASITIC AND TROPHIC INTERACTIONS

Stefan Schuster (Dept. of Bioinformatics, University of Jena)

In numerous interactions between parasites and their hosts, defence and counter-defence mechanisms in the form of toxins and enzymes degrading those toxins can be observed. An example is provided by cephalosporins from Streptomyces clavuligerus, β-lactamases produced by many bacteria and an inhibitor of β-lactamases, clavulanic acid, again secreted by S. clavuligerus. Related phenomena occur in trophic (e.g. plant-herbivore) interactions. Here, we study the question under which conditions it pays, during evolution, to establish a counter-counter defence rather than to intensify or extend the defence. We propose two ODE models based on enzyme kinetics for reversible and irreversible competitive inhibition. We use an objective function based on Haber's rule, saying that the toxic effect is proportional to the time integral of toxin concentration (Area under the curve, AUC). The AUC for a Michaelis-Menten type degradation can be calculated analytically. Here, we calculate, for the case of reversible inhibition, also the optimal allocation to defence and counter-counter defence. Only if the inhibition constant is below a certain threshold, that is, in the case of strong binding, it pays to have a counter-counter defence. A bifurcation is also observed for the dependence on the capacity. For the case of irreversible inhibition, numerical solutions have been derived. Our theoretical predictions should be of interest for computing optimal mixtures of β-lactam antibiotics and β-lactamase inhibitors such as sulbactam in clinical applications, as well as for better understanding plant-herbivore and other molecular-ecological interactions.

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NEARLY ALL PLANTS MUST HAVE CONSTITUTIVE CHEMICAL DEFENSE TO ERADICATE AN ENDEMIC BY GENERALIST INSECTS

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Plants with chemical defenses exist widely in nature. The phenomenon is backed by abundant data, available in plant chemical ecology. Sufficient data are also available to conclude that plant defenses act as deterrent and repellent to attacking herbivores, particularly deleterious generalist insects. Therefore, our objective is to inspect theoretically whether all plant species have to evolve chemical defenses to eradicate the generalists or not.

The objective is addressed by developing deterministic ordinary differential equations under the assumptions: all plants are susceptible to oviposition by generalist insects and total plant population (in a region) is constant throughout the time span of insect attack. From our models, we explicitly obtain that generalists free stable state is possible if approximately all plant species are born with chemical defenses, otherwise not. Therefore, an endemic by generalists is impossible if nearly all plant species become chemically defended in nature.

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MATHEMATICAL DERMATOLOGY LINKING ERUPTION MORPHOLOGY AND SKIN DISEASE

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Chronic spontaneous urticaria (CSU) is one of the most intractable human-specific skin disease that causes red itchy skin eruptions, called wheals, that are of various shapes. These wheals repeatedly appear and disappear daily for up to weeks or even decades, severely impacting the quality of life of those affected. However, as no experimental animal model exists, the mechanism underlying disease pathogenesis in vivo remains unclear, making the establishment of a curative treatment challenging. Here, using a novel approach combining mathematical modeling, in vitro experiments and clinical data analysis, we demonstrate that the pathological state of CSU patients can be inferred by geometric features of the skin eruptions. Based on our hierarchical mathematical modelling, the eruptions of CSU were classified into five categories with distinct histamine, basophils, mast cells and coagulation factors network signatures. The analysis of 105 real CSU patients with this classification by six individual dermatologists achieved 87.6% agreement. The network analysis revealed that the coagulation status likely determines boundary/area pattern of wheals, while the state of spontaneous histamine release from mast cells may contribute to the divergence of size and outline of the eruptions. Our study not only demonstrates that pathological states of diseases can be defined by geometric features but will also facilitate more accurate decision-making to manage CSU in the clinical setting.

PHASE SEPARATION APPROACH FOR INVESTIGATING THE IMPACT OF ORGANIC MOLECULES AND PHOSPHATE IONS ON FORMATION OF BIOSILICA PATTERNS IN DIATOMS

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The formation of regularly structured silica valves in diatoms is a fascinating process in biomineralization. Specific organic molecules, such as long chain polyamines, silaffins, and silacidins, have been found to be essential in this process. The molecular structure of synthesized polyamines significantly affects the amount, size, and morphology of silica precipitates. Experimental findings indicate that silica precipitation occurs at certain concentrations of phosphate ions. When the concentration of phosphate ions is higher, it leads to the formation of larger aggregates of organic molecules that act as templates for the formation of silica.

Our study focuses on the hypothesis that pattern formation in diatom valve structures is driven by the phase separation of species-specific organic molecules, with the evolving organic structures acting as templates for silica deposition. In particular, we focus on the role of phosphate ions in the self-assembly of long chain polyamines and analyze how their reaction with organic molecules impacts the morphology of the organic template. By varying the model parameters, such as the degree of dissociation, the initial concentrations of components, and the growth timescale, we show that the resulting geometric features of the patterns are greatly influenced by these factors.

In addition, we explore the scenario where an initial array of organic droplets serves as a static template for silica deposition, considering the effects of "prepatterning" by the silica costae in the base layer. Furthermore, we extend our model to include the isotropic expansion of the patterning domain and obtain numerical solutions that generate a wide variety of two-dimensional patterns that closely resemble the valve structures observed in experiments.

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CLINICAL CHARACTERIZATION OF MPOX-INFECTED PATIENTS USING A LESION TRANSITION DYNAMICS MODEL

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Mpox is a zoonotic disease caused by the Mpox virus (MPXV) and is endemic in African regions. In July 2022, widespread human-to-human transmission in Europe and North America led to its declaration as a global public health emergency by the WHO. The disease is characterized by lesions similar to those seen in smallpox, appearing throughout the body. These lesions, containing high concentrations of MPXV, facilitate human-to-human transmission upon contact. The lesions undergo various stages, eventually losing infectiousness when the scabs peel off. This study developed a mathematical model to describe the temporal changes in mpox lesion states and analyzed clinical data to quantitatively understand this progression. From March 2007 to August 2011, clinical information from 244 non-sexually transmitted mpox patients was collected in an observational study on MPXV infections. This cohort study took place in a remote area of the tropical rainforest along the Congo River in the Democratic Republic of Congo (DRC) at L'Hopital General de Reference de Kole (Kole Hospital). Using the developed mathematical model, we conducted parameter estimation considering inter-patient variability and reconstructed individual-level lesion state dynamics. We also explored factors characterizing lesion transitions using clinical data, including viral loads for each case. The model of lesion state transition revealed highly heterogeneous dynamics among patients. Specifically, patients were stratified based on the estimated transition dynamics, linking lesion dynamics to viral dynamics. The high viral load in lesions serves as a crucial indicator for clinical infectiousness. Future applications of this study include devising isolation periods and calculating infection transmission probabilities based on these quantitative insights.

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OPTIMAL THERAPY FOR LUNG AND BRAIN CANCERS USING INTRA- AND INTER-CELLULAR NETWORKS

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The therapy of cancer is a long-standing and worldwide issue. Since cancers metastasize to other organs, the treatment method of multiple organs simultaneously is required but it is difficult and has not yet been established. In this study, we investigated an optimal therapy method that targets Notch signaling network which shown in multiple cancers in common. As example studies, we targeted embryonal brain tumor (EBT) and non-small cell lung cancer (NSCSC). Both the two cancers undergo oncogenic development through increased HES1 via Notch signaling, but their signaling pathways of Notch 1 and Notch 2 to enhance HES1 gene have contrastive roles. In NSCSC, Notch 1/2 activates/inhibits cancerization of cells [1]. In contrast, Notch 1/2 plays an opposite role in EBT, namely, Notch 1/2 inhibits/activates the cancerization of cells [2]. To find a possible therapy by which we can treat both cancers at the same time, we developed a conceptual mathematical model based on Notch signaling with the opposite pathways. We explored which network pathway is critical to enhance the cancer cells by sensitivity analysis and found that an intra-cellular pathway is more critical than inter-cellular pathway in enhancing the cancerization of cells and the pathway of Notch transport pathway from cytosol to membrane can be a common network to enhance the cancerization of cells in both cancers. Based on these observations, we also carried out in silico therapy tests for ten patient cases and found that network enhancement therapy is more effective than network cleavage therapy to reduce the number of cancer cells and multiple network therapies are more effective than a treatment of single network therapy. This study suggests that there are optimal signaling network therapies that can treat multiple cancers with contrasting Notch networks and that the simultaneous use of drugs that regulate multiple signaling networks may be most effective in reducing cancer cells.

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NEW CONSERVED QUANTITIES AND MODERN SYMMETRY ANALYSIS APPLIED TO A DISSIPATIVE WESTERVELT EQUATION

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Propagation of sound waves in a compressible medium has several important applications where nonlinear and dissipative effects are relevant. Examples are parametric arrays in water and in air, under water imaging, musical acoustics of brass instruments, sonochemistry, quality control and characterization of materials, and bio-medical devices. Especially significant is ultra-sound imaging in human tissue (see e.g. [1], [2]). A simple mathematical 1D model is given by a dissipative version of Westervelt's equation [3] describing the pressure fluctuation. Symmetries and conservation laws are intrinsic, fundamental aspects of wave equations. Their existence is not precluded by dissipative and nonlinear effects. The present work is devoted to illustrating some of these developments for the dissipative Westervelt equation: -Lie point symmetries of the dissipative Westervelt equation -Conservation laws of the dissipative Westervelt equation -Construction of the potential system -Potential Lie point symmetries -Potential conservation laws -Variational structure

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STUDYING THE BURDEN OF DEPRESSION DURING THE COVID-19 PANDEMIC: AGENT-BASED APPROACH

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During the pandemic of COVID-19, agent-based modeling proved to be a powerful tool for studying the complex multifactorial processes that take place in human population. It is obvious that during this period of time, depression, anxiety and some other mental illnesses were not the focus of public health but the burden of such disorders was increasing. We developed an agent-based model of the city in which the interrelationship between mental health and the level of anxiety caused by both an incidence rate of SARS-Cov2 and the lockdown was simulated. For each agent we determined a number of properties such as age, sex, social status, size of household and state of health based on the official data sources [1]. At the same time, we compile lists of contacts containing family members, classmates or colleagues. As a consequence, all agents are connected in one network. Since the infection we model is airborne, we consider only such type of contacts when people can be at a short distance from each other. For each contact we calculate the probability of infection transmission. Being infected, the agent is supposed to be isolated or hospitalized after the asymptomatic period. Thus, a susceptible agent can become infected only if it has a connection to infected agent. The agent with few contacts could avoid infection as it is with the real infection. We simulated coupled dynamics of COVID-19 and mental disorders during the period between September 2020 and December 2021 in Moscow, Russia. We demonstrated that while the lockdown successfully contributed to slowing down the spread of the virus, the related mobility restrictions were associated with an increased risk of major depressive and anxiety disorders. In addition to the dynamics of the COVID-19 and mental disorders, the burdens of the diseases were assessed by means of quality-adjusted life years (QALY) [2,3]. It can be shown that there is a trade-off between strictness of the lockdown and mental wellbeing.

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ENZYME KINETICS SIMULATION AT THE SCALE OF INDIVIDUAL PARTICLES.

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Enzyme-catalysed reactions involve two distinct timescales. There is a short timescale on which the enzyme binds to a substrate, and a comparatively long timescale over which the resulting bound complex is transformed into a product. The rate at which the substrate is converted into product is characteristically non-linear and is traditionally derived by applying singular perturbation theory to the system's governing equations. This analysis assumes that the enzyme and substrate bind effectively instantaneously when viewed on the long timescale. Many particle-based simulations of reaction-diffusion systems are unable to accurately model this behaviour owing to their use of proximity-based reaction conditions that do not correctly model fast reactions. I will present a new reaction condition that correctly incorporates the fast reactions that occur on the short timescale for a specific enzymatic system, and demonstrate that non-linear reaction rates can be reproduced using proximity-based reaction conditions.

PEST DETECTION FROM A BIOLOGY-INFORMED INVERSE PROBLEM AND PHEROMONE SENSORS

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One third of the annual world's crop production is directly or indirectly damaged by insects. Early detection of invasive insect pests is key for optimal treatment before infestation. Existing detection devices are based on pheromone traps: attracting pheromones are released to lure insects into the traps, with the number of captures indicating the population levels. Promising new sensors are on development to directly detect pheromones produced by the pests themselves and dispersed in the environment. Inferring the pheromone emission would allow locating the pest's habitat, before infestation. This early detection enables to perform pesticide-free elimination treatments, in a precision agriculture framework. In order to identify the sources of pheromone emission from signals produced by sensors spatially positioned in the landscape, the inference of the pheromone emission (inverse problem) is performed. Classical inference is conducted by combining the data and the so-called direct model [1]. In the present case, this entails combining the data from the pheromone sensors and the pheromone concentration dispersion that is a 2D reaction-diffusion-convection model [2]. In the proposed method, the inference involves not only the coupling of the pheromone dispersion model with the pheromone sensors data but also incorporates a priori biological knowledge on pest behaviour (favourite habitat, insect clustering for reproduction, population dynamic behaviour...). This information is introduced to constrain the inverse problem towards biologically relevant solutions. Different biology-informed constraints are tested, and the accuracy of the solutions of the inverse problems is assessed on simulated noisy data.

MATHEMATICAL DEVELOPMENT OF RANDOM MODELS OF HOUSEHOLD INFECTION AND STATISTICAL FITTING TO THREE YEARS OF A LARGE COMMUNITY COVID STUDY

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Households are an important context for understanding infectious disease dynamics due to the typically intense, repeated nature of contacts between individuals sharing living arrangements. During the COVID-19 pandemic, many countries encouraged individuals with detected SARS-CoV-2 infection to isolate at home, breaking contacts outside but not within the household.

Mathematically, infections in households can be modelled in several ways including: numerically tractable systems of differential equations generated by stochastic matrices; calculation of final sizes from solution of sets of linear equations; and Monte Carlo simulation. Each of these poses specific challenges for analysis as well as methods for fitting to data.

Here, I will present novel methods for sequential fitting of final size equations with risk factors to three years of data from the UK Office for National Statistics COVID-19 Infection Survey, a large community study of over 250,000 households. The methods involved allow us to see patterns of non-pharmaceutical interventions, vaccination and strain replacement in during the pandemic in England. The methods involve addition of linear predictors to multitype final-size equations combined with approximate Bayesian inference.

I will also consider new developments for how to deal with complex viral genomic, temporal, and vaccination data that are increasingly available in the household context, combining approaches from machine learning with mechanistic models of transmission.

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UNDERSTANDING PRE-MALIGNANT STEM CELL DYNAMICS: LESSONS FROM CLONAL HEMATOPOIESIS AND STEM CELL TRANSPLANTATION

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The expansion of pre-malignant, i.e. mutated but not yet malignant cells is an important prerequisite for cancer. Multiple factors, including immune dysfunction, inflammation or perturbation of homeostasis, contribute to it. Since pre-malignant cells do not cause symptoms, it is challenging to study them in humans. However, a detailed understanding of their dynamics is required to identify patients at risk for cancer and to counteract malignant transformation. A well-defined scenario to investigate pre-malignant cell dynamics is bone marrow transplantation, a curative treatment option for various diseases of the hematopoietic (blood forming) system. In many healthy subjects a significant proportion of the blood cells are produced by a mutated, potentially pre-malignant stem cell clone. This condition is referred to as clonal hematopoiesis and implies that stem cell grafts often contain mutated cells. In the recipient, these cells can expand, acquire additional hits and trigger donor-derived malignancies. We propose quantitative non-linear ordinary differential equation models to investigate the dynamics of pre-malignant hematopoietic stem cells. The models account for key mechanisms mediating clonal expansion, such as mutation-related changes of stem cell proliferation & self-renewal, aberrant response of mutated cells to systemic signals and chronic inflammation. Combining model simulations, longitudinal patient data and in silico clinical trials, we address the following questions: (i) Why do pre-malignant cells expand in some individuals but not in others? (ii) Why do mutated cells show quick expansion during some time periods and no expansion during others? (iii) How do pre-malignant cells respond to systemic cues such as chronic inflammation & physiological feedbacks? (iv) How do cell-intrinsic and host-specific factors contribute to cell expansion? (v) How can stem cell transplantation protocols be modified to reduce the expansion of pre-malignant cells?

A MATHEMATICAL MODEL OF PHOTOINHIBITION: EXPLORING THE IMPACT OF QUENCHING PROCESSES

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Plants are constantly exposed to changing environments, sometimes leading to extreme conditions and stress. For example, sudden exposure to high light leads to excess absorbed light energy, causing reactive oxygen species (ROS) formation. ROS damage the photosynthetic machinery, particularly the D1 protein in photosystem II (PSII), which therefore needs to be continuously repaired and replaced. The effect of the damage inflicted by high light is a prolonged decrease in photosynthetic efficiency. Hence, it is not surprising that photoinhibition has been subject to numerous experimental studies investigating its effects in the context of crop productivity. However, it has become apparent that classical measures of photoinhibition, i.e., changes in the chlorophyll fluorescence parameter Fv/Fm, are not only determined by the loss of PSII core function but also by processes such as energy transfer and quenching. Mathematical models can help dissect the influences on such fluorescence signals and quantify the contributions of various interacting mechanisms. We present a mathematical model with a dynamic description of the photosynthetic electron transport chain (PETC), non-photochemical quenching, and photoinhibition. With our model, we investigate the interconnection between quenching, photoprotection, and fluorescence using simulations and experimental data. We found that different energy dissipating properties of intact and damaged PSIIs, as well as energy transfer between PSIIs, are critical components that need to be included in the model to ensure a satisfactory fit to the experimental data. We envisage that our model provides a framework for future investigations of photoinhibition dynamics and its importance for plant growth and yield.

MATHEMATICAL MODELLING OF STEM AND PROGENITOR CELL DYNAMICS DURING RUXOLITINIB TREATMENT OF MPN PATIENTS

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Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), including essential thrombocythemia, polycythemia vera, and myelofibrosis, are a group of slowly developing haematological malignancies primarily characterised by an overproduction of myeloid blood cells. Hydroxyurea is a drug which is used for the first line treatment of MPNs. Ruxolitinib, a Janus kinase (JAK) inhibitor, is indicated for the treatment of disease related symptoms in hydroxyurea resistant patients. In this work, we extend previous models describing the disease dynamics of MPNs and the role of inflammation in MPN progression [1]. The extension accounts for ruxolitinib therapy through effects on the malignant stem cell response to cytokine signalling and the death rate of malignant progenitor cells. The model has been fitted to data of individual patients who show a substantial reduction (20 percentage points or 90% of the baseline value) of the malignant cell burden in the clinical trials COMFORT-II [2] and RESPONSE [3] (n=18 and n=6 respectively). The model fits very well to the data with an average RMSE of 0.0250 (2.50%) when allowing the ruxolitinib treatment to affect both malignant stem and progenitor cells. Model simulations and fitting to the data suggest that an initial reduction of the malignant cell burden followed by a monotonous increase can be recapitulated by the model assuming that ruxolitinib affects only the death rate of malignant progenitor cells. For patients exhibiting a long-term reduction of the malignant cells , the model predicts that ruxolitinib also affects stem cell dynamics, such as the malignant stem cells' response to cytokine signalling.

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SYNECHOCYSTIS SP. PCC 6803 PHOTOSYNTHESIS UNDER DIFFERENT LIGHT COLOURS - IN SILICO ANALYSIS

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Well-designed mathematical models complement experimental scientific work. The mathematical representation of reaction networks allows for a detailed and systematic investigation of the system. The network's simplification and breakdown also give a new perspective to working on the whole organism. Cyanobacteria are of high economic value and becoming a promising tool in biotechnological production [1]. However, experimental efforts did not yet lead to a full understanding of how cyanobacteria operate. Furthermore, despite their evolutionary bond to plants, the structure and components of photosynthetic electron transport differ with a high impact on the overall dynamics, prohibiting the usage of established plant-based models. Therefore, targeted mathematical models might be highly beneficial. We have developed an ordinary differential equation-based photosynthesis model in Synechocystis sp. PCC 6803. It dynamically tracks the major photosynthetic processes, from light capture to electron transport and carbon fixation. Notably, we included a full-spectrum light description to mimic lab growth conditions. We used simple kinetic rate laws where no crucial regulatory mechanisms were apparent, and the model was parameterised using dedicated measurements and literature values. With our model, we can reproduce key spectrometric experiments and photosynthetic dynamics. These include the simulated redox state of electron carriers, flux through alternative electron pathways, and dynamic fluorescence signals. We also investigated alternative mechanisms for state transitions, for which no consensus exists yet. Notably, the model showed that the irradiance light colour determines the distribution of metabolic control and, therefore, biotechnological targets. With this model, we integrate systems-level knowledge of photosynthesis in cyanobacteria and provide a theoretical framework for further complex investigation.

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MATHEMATICAL MODELLING OF THYROID HORMONE DYNAMICS IN HYPO- AND HYPERTHYROIDISM

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We present a 9 differential equation model of thyroid hormone dynamics that explicitly models the concentrations of the prinicipal hormones, the plasma transporters, and binding and unbinding. We show that a reduced model of just four equations is sufficient to accurately reproduce the dynamics of the principal hormones displayed in the 9-differential equation model, but that further reductions to models with just 2 or 3 equations do not capture the dynamics of the full model. We use a modification of the 4 equation model to study hypo- and hyperthyroidism, two of the most common human auto-immune diseases. We simulate free thyroxine (FT4), free triiodothyronine (FT3) and thyroid-stimulating hormone (TSH) concentrations with and without levothyroxine (LT4) supplementation, showing that FT4 concentrations take several weeks to stabilise after a change of dose. We use the model to create a dosing grid from which the current FT4 concentration and LT4 dose are used to determine a new dosing range to bring the FT4 concentration into the target range. Although our model has a number of limitations, our results suggest that it could be feasible to develop personalised models of thyroid hormone dynamics and treatment.

TARGETING CELLULAR EXHAUSTION AS A MEANS TO POTENTIALLY IMPROVE IMMUNOTHERAPEUTIC EFFORTS AGAINST SOLID TUMORS.

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T cell exhaustion is a form of cellular dysfunction initiated by chronic inflammation and prolonged stimulation and is often associated with chronic infections and cancer. Exhausted T cells are characterized phenotypically by an upregulation of inhibitory receptors and have been observed to show diminished effector functions. In cancer settings, these dysfunctional immune responses result in a tumor-immune stalemate. Targeting exhausted T cells as a form of immunotherapy has shown promising, albeit inconsistent, results. It is also important to note that T cell exhaustion has also been linked to the ineffectiveness of other forms of cancer therapy. Through the use of mathematical modeling, the dynamic system of T cell exhaustion in response to a growing solid tumor is reconstructed. Analysis of this mathematical framework highlight the functional abilities of such dysfunctional cells and the ensuing stalemate. Cellular species, and more specifically, particular functions of such cells, have also been identified to have the largest impact on tumor growth and control. Taken together, this project identifies the type of cells and the specific functions that should be the focus of further research to help guide the development of future immunotherapeutic efforts.

IMPACT OF BIODIVERSITY LOSS ON THE STRUCTURE AND STABILITY OF A MARINE ANTARCTIC FOOD WEB

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The consequences of climate change and anthropogenic stressors, such as habitat loss and overexploitation, are threatening the subsistence of species and communities across the planet. Therefore, it is crucial to analyze the impact of environmental perturbations on the diversity, structure and function of ecosystems. In this study, we carried out in silico simulations of biodiversity loss on the marine food web of Potter Cove (25 de Mayo/King George Island, Antarctica) where global warming has caused critical changes in the abundance and distribution of benthic and pelagic communities during the last 30 years. We performed species removal considering their degree and trophic level and including four different thresholds on the occurrence of secondary extinctions. We examined the impact of extinctions on connectance, modularity and stability of the food web. We observed that removing most connected and relatively high-trophic level species caused rapid changes in modularity and stability. In addition, we studied the complexity-stability relationship of the food web and found two regimes: 1) high sensitivity to small perturbations suggesting that Potter Cove would be locally unstable, and 2) high persistence to long-range perturbations suggesting global stability of this ecosystem.

CAN AGE-BASED RESTRICTIONS REPLACE HORIZONTAL LOCKDOWNS?

Vasilis Tsilidis (Department of Mathematics, University of Patras)
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During a pandemic, such as the recent COVID-19 health crisis, policymakers are confronted with the decision of implementing effective, yet socioeconomically detrimental measures, such as horizontal lockdowns, which encompass school and workplace closures, physical distancing, and other similar measures. Age-based restrictions have been discussed as a possible alternative to horizontal restrictions. In light of the above statement, we propose a novel age-structured SVeaiR epidemiological model, along with a scheme for the comparison of certain epidemiological strategies. We investigate the global stability of the model and put the scheme to the test, in order to compare the effectiveness of age-based and horizontal restrictions.

A NETWORK TRANSPORT MODEL FOR THE PROGRESSION OF ALZHEIMER'S DISEASE

Veronica Tora (University of Rome "Tor Vergata", Rome, Italy)
Other authors: M. Bertsch, A. Raj , J. Torok

The accumulation and spread of toxic tau protein is one of the main hallmark of Alzheimer's disease (AD). The progression of AD tau pathology is thought to be highly stereotyped, since tau can spread between regions via the white matter tracts that connect them. However, an underexplored aspect of tau spreading is that it is governed not simply by diffusion but also active transport along axonal microtubules. Spread can therefore take on a directional bias, resulting in distinct patterns of deposition. A two neurons mathematical model of the axonal transport of toxic tau protein has been recently developed in [1]. In this talk, we present a macroscopic model, called Network Transport Model (NTM), which combines the dynamics of soluble and insoluble tau in the gray-matter regions and the axonal transport model [1] in the white-matter tracts. This model enables us to simulate the dynamics of soluble and insoluble tau in terms of the diffusion-advection and aggregation-fragmentation processes at the network level. More precisely, the full network model involves a transport-reaction PDE on each edge and a diffusion-reaction equation on the nodes describing tau dynamics in the gray matter regions. A straightforward mass transfer mechanism of soluble tau between edges and nodes determines the incoming flux of soluble tau into the nodes. However, the full NTM is computationally infeasible to simulate on the full network, thus we provide and implement a quasi-static approximation to the NTM that maintains the basic properties of the full NTM and is more tractable numerically. Here, we present the main features of the quasi- static NTM and we will show some numerical simulation which demonstrate that the quasi-static NTM expands the range of behaviors that can be exhibited with previous models, particularly in terms of directionally biased flows on the connectome and thus such approach is effective in understanding key mechanisms of AD progression.

[1] Torok, Justin et al. (2021). Emergence of directional bias in tau deposition from axonal transport dynamics. PLOS Computational Biology, 17(7), e1009258.
https://doi.org/10.1371/journal.pcbi.1009258

SULFUR MEDIATED PRECIPITATION IN A BIOFILM REACTOR

Vincenzo Luongo (Department of Mathematics and Applications "Renato Caccioppoli", University of Naples Federico II)
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Microbial life predominantly undergoes evolution in the form of biofilms, which are microorganism colonies embedded in a self-produced matrix, actively interacting with their surrounding environment. The use of mathematical modeling in biofilm systems is crucial for comprehending microbial life evolution and its intricate interactions in biofilm reactors. For instance, metallic inorganic particles in water have the ability to interact with these living systems and deeply influence diverse biotechnological applications of biofilms. This research introduces a mathematical model adept at elucidating the growth and evolution of a multispecies biofilm thriving in a trace metals rich environment. The study places particular emphasis on the occurrence of chemical precipitation phenomena within the biofilm's inner regions under specific environmental conditions. The biofilm structural space availability and the physico-chemical attributes of the surrounding environment emerge as pivotal factors influencing the biologically mediated precipitation process. The model formulation encompasses a system of first-order quasi-linear hyperbolic equations delineating the biofilm components' growth, a set of diffusion-reaction equations governing soluble compounds, and a nonlinear ordinary differential equation characterizing the biofilm thickness. This latter represents the dynamic evolution of the biofilm free boundary domain . Numerical applications underscore the model's accuracy in faithfully reproducing the accumulation of precipitates within real-case biofilm systems.

ECO-EVOLUTIONARY DYNAMICS IN FINITE NETWORK-STRUCTURED POPULATIONS WITH MIGRATION

Wajid Ali (University of Liverpool, UK)
Other authors: K. Pattni, M. Broom and K. J. Sharkey

In this talk, I will briefly introduce evolutionary graph theory which studies the dynamics of mutant gene in finite network-structured populations. While sophisticated, the this framework has limitations, such as fixed population size and distribution, and coupled birth and death processes. Addressing these gaps, we explore eco-evolutionary dynamics, allowing for dynamic changes in population size and distribution through separate birth, death, and migration processes. Considering network structure, we analyse the success of mutants in rare mutation scenarios for complete, cycle, and star networks. Our approach models individual distribution dynamics, determining mutant appearance distributions and revealing network-specific impacts on mutant success, providing insights into the interplay of network structure, migration, and eco-evolutionary outcomes in finite populations.

[1] Pattni, K. et al. (2023). Eco-evolutionary dynamics in finite network-structured populations with migration. Journal of Theoretical Biology, 572(1), 111587.
https://doi.org/10.1016/j.jtbi.2023.111587

DRUG-RESISTANT BACTERIUM PSEUDOMONAS AERUGINOSA VS. HOST: NESTED DEFENCE STRATEGIES

Wassili Dimitriew (Friedrich Schiller University Jena)
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Pseudomonas aeruginosa, a versatile Gram-negative bacterium, has emerged as a significant human pathogen, capable of causing various infections. In the World Health Organization's priority list of antibiotic-resistant bacteria, which underscores the urgent need for research and development of novel antibiotics, P. aeruginosa has the highest, "critical" priority level [1]. Its adaptability to diverse environments renders it a persistent menace in various clinical settings. One remarkable aspect of this adaptability is P. aeruginosa's ability to survive within macrophages, resulting from nested defence strategies, where both the host and the pathogen evolve mechanisms to counter each other's actions.

For instance, P. aeruginosa employs a mechanism for itaconic acid (or itaconate) degradation [2], representing a rare instance of counter-counter-counter defence. We developed a minimal model to elucidate the interplay of P. aeruginosa and its macrophage host. Employing a quasi-sequential approach to dynamic optimization [3], we investigated the temporal dynamics of the counter-defence and counter-counter-counter defence as well as the corresponding optimal resource allocation from the pathogen's perspective under different infection scenarios. This approach not only facilitated a deeper comprehension of the P. aeruginosa infection process but also led to hypotheses regarding novel strategies to combat this infection. Consequently, we were able to show that an elaborated regulation is superfluous for the itaconate degradation process, and that the putative presence of such a regulation could indicate the existence of even higher degrees of the nested defence strategy.

[1] Tacconelli, E. et al. (2017). Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. The Lancet Infectious Diseases, 18(3), 318-327. https://doi.org/10.1016/S1473-3099(17)30753-3
[2] Sasikaran, J. et al. (2014). Bacterial itaconate degradation promotes pathogenicity. Nature Chemical Biology, 10(5), 371-377. https://doi.org/10.1038/nchembio.1482
[3] Bartl, M., Li, P., Biegler, L.T. (2010). Improvement of state profile accuracy in nonlinear dynamic optimization with the quasi-sequential approach. AIChE Journal, 57(8), 2185-2197. https://doi.org/10.1002/aic.12437

THE ROLE OF BACTERIAL DILUTION AND STOCHASTIC GROWTH IN VIBRIO FISHERI SYMBIOTIC COLONIZATION

Xabier Rey Barreiro (Nonlinear Control group, Department of Systems and Control Engineering, Universidade de Vigo)
Other authors: A.F. Villaverde, L. Fant

This study addresses the challenge of understanding the symbiotic colonization of the squid, Euprymna scolopes, by bioluminescent bacterium Vibrio fischeri. Previous research such as [1][2] has tried to shed light on the complex dynamics of these two organisms. Through colonization, the squid manages to produce light (which helps it evade predators), while bacteria obtain a nutrient-rich environment for growth. Nonetheless, V. fischeri can develop a mutation that stops light production, resulting in a fitness advantage. This leads to a situation usually called "tragedy of the commons" where, even though cooperation is generally advantageous, it fails to be stable given the advantage of cheaters [3]. Intriguingly, this is not the case. This observation leads to crucial questions: how can squids prevent mutant population to invade? What mechanisms have evolved to maintain a symbiosis free of mutants? The symbiotic relationship between squids and bacteria involves mechanisms like daily bacterial dilution by squids, which may have a more significant impact than is generally thought in microbiology. Our hypothesis suggests that bacterial dilution and multiplicative random growth, both well-documented phenomena, might play essential roles in preventing mutant proliferation. Our goal is to shed light on how these processes influence the growth of smaller populations within a competitive system. To this end, we built a mathematical model of the system, which describes how the aforementioned mechanisms influence the competition and coexistence of bacterial species. We find that stochasticity in both growth and dilution lowers the invasion probability of cheaters. Dilution thus proves to be an effective mechanism to control the genetic variability of bacteria. We think that the insights from this study not only advance our understanding of this symbiosis but also have broader implications in managing bacterial invasions in diverse ecological environments.

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[2] Ruby, E. G, McFall-Ngai, M. J (2002). Oxygen-utilizing reactions and symbiotic colonization of the squid light organ by Vibrio fischeri. Trends in Microbiology, 7(10), 414-420.
https://doi.org/10.1016/S0966-842X(99)01588-7
[3] Fant, Lorenzo et al. (2023). Stable cooperation emerges in stochastic multiplicative growth. Physical Review E, 108(1). https://doi.org/10.1103/PhysRevE.108.L012401

SPATIAL DISTANCING: MODELING IMMUNE EVASION BY THE HUMAN-PATHOGENIC FUNGUS CANDIDA ALBICANS

Yann Bachelot (Applied Systems Biology, Leibniz-Institute for Natural Product Research and Infection Biology, Hans-Knöll-Institute (HKI), Germany)
Other authors: A. Solomatina, P. Rudolph, S. Timme, M. T. Figge

Understanding the complex interplay between host and pathogen during infection scenarios is critical to the development of improved diagnostics and therapeutic interventions. Among the diverse arsenal employed by the host, antimicrobial peptides (AMPs) play a crucial role in the defense against pathogens. However, some pathogens, such as the yeast Candida albicans, have developed strategies to evade the immune response.

In this study, we use a modeling approach to investigate an immune evasion mechanism, which we refer to as spatial distancing. To achieve spatial distancing, the pathogen secretes defense molecules that can bind to AMPs and form complexes that diffuse away from the pathogen. As a result, AMPs are transported away from the pathogenic cell surface, protecting it from the immune attack by AMPs. This mechanism has been studied in vitro in C. albicans [1], where it was shown that it also confers protection to other species in co-infection scenarios.

To gain a comprehensive understanding of this immune evasion mechanism, we simulated a pathogenic cell in a three-dimensional environment with molecule concentrations modeled by partial differential equations. Two different scenarios were simulated, respectively, representing AMPs secreted by immune cells and AMPs administered for medical treatment. Spatio-temporal distributions of molecules reveal a reduction in the concentration of AMPs in the vicinity of the pathogen, indicating the efficacy of spatial distancing. Systematic screening of parameters demonstrates the robustness of this mechanism, consistently showcasing a beneficial regime for the pathogen's survival.

Our findings underscore spatial distancing as an effective countermeasure employed by pathogens to resist the antimicrobial actions of AMPs. The inhibition of molecules secreted by the pathogen in defense against the AMPs could be a possible target for therapeutic interventions.

[1] Szafranski-Schneider, E. et al. (2012). Msb2 Shedding Protects Candida albicans against Antimicrobial Peptides. PLoS Pathogens, 8(2), e1002501.
https://doi.org/10.1371/journal.ppat.1002501

BACKWARD BIFURCATION AND PERMANENCE OF DISEASE-SEVERITY-STRUCTURED EPIDEMIC MODELS WITH TREATMENT CAPACITY

Yasuhisa Saito (Department of Mathematics, Shimane University)

When an unknown pathogen is encountered, developing medicines and vaccine to counter its effects becomes a potentially urgent task. In addition to these primary medical issues, there exists a secondary problem of medical collapse; it is caused by limited treatment capacity that includes limited number of medical supplies, doctors, nurses, beds, and other medical equipment, and must be seriously considered from a public health perspective. To discuss the effects of treatment capacity on disease transmission, we present disease-severity-structured epidemic models with necessary treatment only for severely infective individuals. We demonstrate the occurrence of backward bifurcation, wherein a stable endemic equilibrium coexists with a stable disease-free equilibrium when the basic reproduction number is less than 1, and if the treatment capacity is relatively small. This epidemiological implication states that when there is insufficient capacity for treatment, having the basic reproduction number less than 1 is not enough for effective disease control; the outbreak can reach a high endemic level even in such cases. The permanence of our model, signifying uniform strong disease persistence, is also discussed when the basic reproduction number exceeds 1.

UNDERSTANDING THE BIASED DISTRIBUTION IN TRACTION FORCES IN COOPERATIVE CELL MOTILITY

Ying Zhang (Northeastern University)
Other authors: C. Copos

Streams of migratory Dictyostelium cells are initiated by the formation of tandem pairs of cells connected head to tail to which other cells and subsequently adhere. Interestingly, when cells migrating in tandem pairs the dynamics of the traction forces exhibit two distinct patterns with a significant bias in their occurrences. In about 80% of the time each cell in the migrating tandem pairs generates a contractile traction force dipole, maintaining the traction force signature of the single cell case. In about 20% of the time the two cells fuse into a single contractile traction force dipole. Although previous experimental works suggested linking the pair mechanically, it remains unclear what are the contributing factors that lead to this bias. In this work, we develop a model to explain the emergence of the biased distribution traction forces mechanistically. As the mechanism at the cell-cell junction with the environment in Dictyostelium cells is unknown, we will use both a 2D model and a simplified model to reveal the mechanical coupling at the cell-cell junction that gives rise to this bias.

MODELING INTRA- AND INTER-HOSPITAL TRANSMISSION OF MIDDLE EAST RESPIRATORY SYNDROME AND PREVENTIVE STRATEGY

Youngsuk Ko (Department of Mathematics, Konkuk University, Korea)
Other authors: Eunok Jung

The outbreak of Middle East Respiratory Syndrome (MERS) in South Korea in 2015 was the largest outbreak outside of endemic regions. Despite the nature of the disease, which was not expected to have a large scale outside of endemic areas, a total of 186 confirmed cases (38 of them died) occurred due to the delay in disclosing the exposed hospitals and the active culture of hospital visits. In this presentation, a modeling study of the MERS outbreak considering intra- and inter-hospital transmission will be presented, including realistic simulation results based on Korea. In addition, a quantitative study on how effectively the wearing of masks in hospitals, which has become a normal after the COVID-19 pandemic, prevents the transmission of infectious diseases will also be introduced.

[1] Lee, S.M. et al. (2018). Psychological impact of the 2015 MERS outbreak on hospital workers and quarantined hemodialysis patients. Comprehensive Psychiatry, 87(1), 123-127. https://doi.org/10.1016/j.comppsych.2018.10.003

ESTIMATION OF THE CELL-TO-CELL TRANSMISSION RATE USING A SPATIO-TEMPORAL MATHEMATICAL MODEL

Yusuke Asai (National Center for Global Health and Medicine)

Viral dynamics in our bodies have been described by the interaction between viruses, susceptible cells and infected cells. The efficacy of therapeutic agents and the optimisation of treatment schedules have been discussed on the basis of the mathematical model, but most models assume that infection is caused by free viruses, i.e. viruses circulating in the body. It has been reported that cell-to-cell transmission can transfer large amounts of virus at once, which is crucial when we estimate the transmission rate of viruses. In this study, we first consider an ordinary differential equation system consisting of four compartments, target cells, exposed cells, infectious cells and dead cells. The infection process is then approximated by a Taylor expansion and the cell-to-cell transmission is given by the derivatives up to the second order, i.e. the diffusion term. The developed partial differential equation model is discretised and given in both Gaussian and polar coordinates, and applied to in vitro data to estimate the transmission rate and the death rate, essential parameters that determine the dynamics of the infection process. A travelling wave is a wave that travels in a given direction in a given space. The existence of the travelling wave in an infectious disease model means that the area of infection is constantly expanding. Therefore, it is important to find the travelling wave solution. We further investigate the condition for the existence of the travelling wave solution under the given system.

[1] Kim, Kwang Su et al. (2020). Modeling the efficiency of filovirus entry into cells in vitro: Effects of SNP mutations in the receptor molecule. PLOS Computational Biology, 16(9), e1007612. https://doi.org/10.1371/journal.pcbi.1007612

MOMENT-BASED INFERENCE OF STOCHASTIC REACTION NETWORKS WITH ERROR GUARANTEES

Zekai Li (Imperial College London)
Other authors: Mauricio Barahona, Philipp Thomas

Stochastic reaction networks are used in many fields to model the behaviour of complex systems with uncertainty. Inference of the rate parameters in these networks is an essential and challenging task for accurately understanding the network. While numerous inference methods have been proposed and implemented, the uncertainty measures associated with these methods often lack theoretical guarantees. Here, we propose a novel inference approach to obtain rigorous bounds on the parameters via convex optimisation over sets constrained by moment equations and moment matrices. Our approach takes observations from the stochastic network at steady state and forms moment intervals using the bootstrap method which are then used in the constrained sets. Under the condition that the moment intervals, obtained through bootstrap from the original data, contain the true stationary moments, our bounds on the parameters are guaranteed to contain the true parameters. Our method is also applicable in cases where latent species or observation errors exist. In the former case, we can also bound the stationary moments of the latent species.

HOW CENTRALITY MEASURES CAN REDUCE COMPLEXITY OF ELEMENTARY CONVERSION MODES - OPPORTUNITIES CONNECTING NETWORK SCIENCE AND METABOLIC MODELS

Zita Soons (University Hospital RWTH Aachen)
Other authors: A. Berger, O. Bay, L. Kuepfer

Motivation. The description of a metabolic network in terms of elementary conversion modes (ECMs) provides an promising framework for metabolic flux analysis by establishing all overall conversions that span the space from nutrients to new cells and the secretion of products [1]. However, the enumeration of the full set of ECMs for genome-scale metabolic networks or communities of microorganisms has been infeasible. Complementary strategies from network science are feasible on a large-scale, albeit their integration in metabolic flux prediction has achieved mixed success. We will discuss how network theory can be used successfully to reduce complexity. Results. The calculation time and the number of ECMs depend on the number of external metabolites. The complexity can be reduced by focusing on the conversions between user-defined subset of external metabolites, the "hide" option. However, we do not know a priori which metabolites are important for a new microbial strain. We systematically evaluate the conversion space spanned by ECMs by evaluating network measures for all possible combinations of substrates and products and compare this to the original conversion space. For these subsets of metabolites, we also compute network measures based on the average change of centrality of the network. In order to accurately describe the potential interactions between microbes by uptake and production of metabolites, we aim to find subsets of metabolites that keep a high coverage of the conversion space by ECMs based on the average change of centrality of the network. In our presentation, will demonstrate the methods using the E. coli core model and show applications using reconstructed GSMNs of strains Oligo-Mouse Microbiota 19.1 found in the gut.

[1] Clement, T.J. et al. (2020). Unlocking Elementary Conversion Modes: ecmtool Unveils All Capabilities of Metabolic Networks. Patterns, 2(1), 100177.
https://doi.org/10.1016/j.patter.2020.100177

MINI-SYMPOSIA

MATHEMATICAL MODELS FOR VECTOR-BORNE INFECTIONS

Christopher Kribs, Andrea Pugliese

Vector-borne infections have been one of the main sources of mortality and morbidity (for example, malaria or dengue) in tropical countries. Ongoing climate change suggests that this problem may extend to new areas, and indeed several instances have been reported of autochthonous transmission in European countries of mosquito-borne infections (West Nile, Chikungunya, dengue). Understanding the dynamics of such infections involves coupling the typical methods of infectious disease modelling to models of the population dynamics of vectors (and often of non-human hosts) under the influence of abiotic conditions and ecological interactions. This mini-symposium will consider different approaches to modelling vector-borne infections, from the use of differential equations to statistical data-driven models.

THE IMPACT OF INFESTATION BEHAVIORS ON VECTOR-BORNE DISEASE: CO-FEEDING TRANSMISSION DYNAMICS

Jianhong Wu (York University, Canada)

We present a short summary of some recent studies on vector-borne disease transmission dynamics through both systemic transmission and co-feeding transmission. As the co-feeding transmission occurs when infected and uninfected vectors (perhaps at different development stages) feed in spatiotemporal proximity to each other on the same host, the transmission efficiency depends on the vector attachment and host grooming behavior that generates spatiotemporal infestation patterns. The transmission dynamics is appropriately described by multiple-scale models involving the infestation dynamics at the individual level and transmission dynamics in the population level.

EVALUATING THE TRANSMISSION DYNAMICS OF CO-CIRCULATING CHIKUNGUNYA, ZIKA, AND DENGUE VIRUSES

Alex Perkins (University of Notre Dame, USA)

The co-circulation of chikungunya, Zika, and dengue viruses constitutes an expanding health threat in tropical and subtropical regions. The similarity among their diseases' clinical manifestation induces a broad range of misdiagnosis among the cases, and challenges intervention strategies when they rely on clinically diagnosed cases. By developing a deterministic compartmental model which accounts for the co-circulation of chikungunya, Zika, and all dengue serotypes, we assess different factors that can alter the diseases' trajectories when chikungunya, Zika, and dengue co-circulate. Our study reveals that the interaction between two viruses not only alters their disease dynamics but also influences the circulation of other viruses through the susceptible population and the viruses' introduction times. Importantly, misdiagnoses among these viruses can significantly skew estimates of key parameters, such as the initial prevalence of infection and the probability of apparent disease. This, in turn, leads to counterfactual projections of the diseases, undermining the accuracy of public health assessments and intervention strategies. Our findings support the necessity of a unique disease definition that distinguishes chikungunya, Zika, and dengue.

MODELLING THE CLIMATE-DRIVEN TRANSMISSION SUITABILITY OF THE DENGUE VIRUS

José Lourenço (Católica University and University of Lisbon, Portugal)

Over the past 5 years, our team has been developing and implementing a modelling technique that aims at estimating the climate-driven transmission suitability of the dengue virus. While there are already several successful implementations of the technique, we are far from holding the perfect modelling solution. In this talk, we will introduce the ideas behind the modelling technique, its success stories, existing pitfalls, current research initiatives, and opportunities for future advances.

IMPACT OF ADE AND DENGUE VACCINATION WITH SCREENING ON THE TOLL OF A DUAL DENGUE-ZIKA OUTBREAK

Christopher Kribs (University of Texas at Arlington, USA)
Other authors: D. Greenhalgh

The tetravalent dengue vaccine Dengvaxia may prime dengue-seronegative vaccinees for antibody-dependent enhancement (ADE) of any subsequent dengue (in case of vaccine failure) or Zika infections. Many researchers associate ADE of such cases with more severe outcomes including death. This talk uses a mathematical model of transmission dynamics that distinguishes ADE and non-ADE cases for each virus, to identify the potential impact of a dengue vaccination campaign on the economic cost and disease burden of a dual dengue-Zika outbreak,

under the hypothesis that severe outcomes are associated with ADE. Results indicate that when all dengue exposure is to a single serotype, in most cases vaccination increases both cost and burden because they are dominated by the high costs associated with complications from ADE Zika cases. However, if per-case ADE Zika costs are lower than estimated (a real possibility given the limited data available), sufficiently high vaccination coverage can reduce total cost and burden substantially. Analysis also identifies variations across countries, dengue serotypes, and timeframes of evaluation.

[1] Kribs, C., Greenhalgh, D. (2023). Impact of tetravalent dengue vaccination with screening, ADE, and altered infectivity on single-serotype dengue and Zika transmission. Journal of Mathematical Biology, 86(5). https://doi.org/10.1007/s00285-023-01915-7
[2] Kribs, C. (2023). Impact of dengue vaccination choice on Zika risk: free riders and the tragedy of the commons. Epi-SCIENCE, 1(1). https://doi.org/10.15517/es.2023.55392

MODELING THE RISK OF ARBOVIRAL TRANSMISSION AT DETAILED SPATIO-TEMPORAL SCALES

Piero Poletti (Fondazione Bruno Kessler, Italia)

Estimates of the spatiotemporal distribution of different mosquito vector species and the associated risk of transmission of arboviruses are key to design adequate policies for preventing local outbreaks and reducing the number of human infections in endemic areas. In this study, we quantified the abundance of Aedes albopictus and Aedes aegypti and the local transmission potential for three arboviral infections at an unprecedented spatiotemporal resolution in areas where no entomological surveillance is available. We developed a computational model to quantify the daily abundance of Aedes mosquitoes, leveraging temperature and precipitation records. The model was calibrated on mosquito surveillance data collected in 115 locations in Europe and the Americas between 2007 and 2018. Model estimates were used to quantify the reproduction number of dengue virus, Zika virus, and chikungunya in Europe and the Americas, at a high spatial resolution. In areas colonised by both Aedes species, A aegypti was estimated to be the main vector for the transmission of dengue virus, Zika virus, and chikungunya, being associated with a higher estimate of R0 when compared with A albopictus. Our estimates highlighted that these arboviruses were endemic in tropical and subtropical countries, with the highest risks of transmission found in central America, Venezuela, Colombia, and central-east Brazil. A non-negligible potential risk of transmission was also estimated for Florida, Texas, and Arizona (USA). The broader ecological niche of A albopictus could contribute to the emergence of chikungunya outbreaks and clusters of dengue autochthonous cases in temperate areas of the Americas, as well as in mediterranean Europe (in particular, in Italy, southern France, and Spain). Our results provide a comprehensive overview of the transmission potential of arboviral diseases in Europe and the Americas, highlighting areas where surveillance and mosquito control capacities should be prioritised.

[1] Zardini, A. et al. (2024) Estimating the potential risk of transmission of arboviruses in the Americas and Europe: a modelling study. Lancet Planet Health. 8(1):e30-e40. https://doi.org/10.1016/S2542-5196(23)00252-8

SPATIOTEMPORAL DYNAMICS OF ARBOVIRUS TRANSMISSION AND CONTROL

Victoria Cox (Imperial College London, UK)

MATHEMATICAL INSIGHTS INTO TELOMERE LENGTH DYNAMICS

Marie Doumic, Denis Villemonais

Telomeres are specialised non-coding double-stranded repetitive DNA-protein complexes that form protective caps on the ends of chromosomes. They safeguard their extremity and maintain genomic integrity by allowing cells to distinguish telomeres from sites of DNA damage. Telomere length displays progressive shortening in replicating cells with age. Eventually cells will acquire critically short and dysfunctional telomeres that, consequently, activate a DNA damage response and growth arrest known as replicative senescence. Therefore, all somatic cells have limited cell proliferation capacity called the Hayflick limit.

In the human body, shortened telomeres are related to the occurence of degenerative, age related diseases. Telomeres lengths at early stages of an individual's life are determined by numerous factors, including the parent's telomere lengths, environmental factors and other predisposition, whose exact nature remains to be determined.

In yeast, the mechanisms of telomere attrition and specific telomere lengthening give rise to specific population dynamics, which relate to open questions in biological studies.

As a consequence, it is of crucial importance to develop an efficient model for telomere length dynamics, both in the human body and in yeast, to test and understand different hypotheses for the cause and consequences of abnormally short telomeres.

The aim of this mini-symposium is to present recent results in the mathematical and numerical modelling of telomere dynamics in a population of cells, and on statistical estimation of biologically relevant parameters for telomere length dynamics.

STOCHASTIC BRANCHING MODEL FOR THE TELOMERES DYNAMICS INCLUDING TELOMERASE

Coralie Fritsch (Inria, Nancy Grand-Est, team project SIMBA, France)
Other authors: A. Benetos, E. Horton, L. Lenôtre, S. Toupance, D. Villemonais

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Telomeres are short sequences of nucleotides at the end of chromosomes, whose evolution over time is intrinsically related to biological ageing. In most somatic cells, with each cell division, telomeres shorten due to the so-called end replication problem, which can lead to replicative senescence and a variety of age-related diseases. On the other hand, in certain cells, the presence of the enzyme telomerase can lead to the lengthening of telomeres, which may delay or prevent the onset of such diseases but can also increase the risk of cancer. In this talk, we propose a stochastic branching model of the telomeres dynamics in a cell population, which

may include telomerase. We study the asymptotic behavior of the population and numerically illustrate the impact of the model parameters (for example the number of chromosoms in each cell and the telomerase parameters) in the survival/extinction of the population, the asympotic growth rate as well as the asymptotical distribution of the telomere lenghts in cells.

STATIONARY DISTRIBUTION OF TELOMERE LENGTHS IN CELLS WITH TELOMERE LENGTH MAINTENANCE AND ITS PARAMETRIC INFERENCE

Marek Kimmel (Rice University, Texas, United States)

Professor Marek Kimmel has accepted to present his recent research in telomere dynamics in our mini-symposium. This research includes, among other, the paper *Stationary Distribution of Telomere Lengths in Cells with Telomere Length Maintenance and its Parametric Inference*, in collaboration with Kyung Hyun Lee [1].

[1] Lee, K. H., Kimmel, M. (2020). Stationary Distribution of Telomere Lengths in Cells with Telomere Length Maintenance and its Parametric Inference. Bulletin of Mathematical Biology, 82(12). https://doi.org/10.1007/s11538-020-00811-1

AN INVERSE PROBLEM IN CELL DYNAMICS : ESTIMATING THE INITIAL DISTRIBUTION OF TELOMERE LENGTH FROM THE MEASUREMENTS OF SENESCENCE TIMES

Jules OLAYÉ (Ecole Polytechnique, France)
Other authors: M. Doumic

Telomeres are repetitive sequence situated at both ends of chromosomes of eukaryotes cells. At each cellular division, they are eroded, until reaching a state where the cell does not divide anymore : the senescent state. In this work, we are interested in the link between the initial distribution of telomeres, and the distribution of senescence times. We give two methods that allow to retrieve the initial distribution of telomere length, by having only measurements of senesence times. First, we obtain two approximations for the PDE of our model : an approximation by a transport equation, and an approximation by an advection-diffusion equation. Then, we solve the inverse problem on each of the approximations. In particular, in the advection-diffusion equation approximation, we find a link between the Laplace transforms of the initial distribution of telomere length, and the Laplace transform of senescence times. Using the Gaver-Stehfest algorithm, which is an algorithm that allows to numerically inverse a Laplace transform, we are then able to obtain an estimation of the initial distribution of telomere length, from the

measurements of senescence times.

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INDIVIDUAL CELL FATE AND POPULATION DYNAMICS REVEALED BY A MATHEMATICAL MODEL OF REPLICATIVE SENESCENCE

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Most human cells, or experimentally mutated cells, have a limited replication capacity that originates in the shortening of the extremities of their chromosomes, the telomeres, during DNA replication. When telomeres reach a critical length, the cell recognizes it as a DNA damage which triggers replicative senescence, an irreversible arrest in the cycle, eventually leading to cell death.

While the population scale is the most relevant to study telomere-related in vivo dynamics (tissue development and renewal, aging, cancer emergence), population experiments often lack precise measurements. Conversely, microfluidic experiments, which track single cell lineages, prove very informative. In yeast, they reveal that senescence is highly heterogeneous. For example, lineages enter senescence at various generations and times, and through distinct pathways: some experience transient arrests - i.e. abnormally long cycles followed by a return to normal ones- before entering senescence [1].

Such heterogeneity, besides promoting genome instability and senescence escape, generates non-trivial selection and competition effects in population, which are not captured by lineage (microfluidic) data. To decipher the experimentally hidden complexity of the dynamics at play within senescent populations we mathematically model the replicative senescence in yeast. Building on previous works, our model accounts not only for the intracellular telomere-shortening mechanisms [2], at the origin of senescence, but also the apparently stochastic appearance of transient arrests [3].

After having introduced the biology and the model, we will focus on a few results. First, we will discuss the calibration of the model on microfluidic data, which suggests that transient arrests would drastically alter the way telomere lengths trigger senescence onset. Simulating the model will allow us to access experimentally hidden quantities and study the influence of specific parameters on population dynamics.

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GENETIC AND NON-GENETIC ROUTES TO PHENOTYPIC PLASTICITY IN CANCER

Carmen Ortega-Sabater, Mohit K. Jolly

Genomic instability is one of the hallmarks of cancer and this broad concept involves changes in several layers that must be integrated to properly understand cancer initiation and progression. These layers include changes in chromatin; alterations in DNA replication, transcription, and translation; and epigenetic modifications. Although all of these have been carefully preserved by selection and evolution across species, they are altered in some scenarios such as ageing or cancer development. Mutations and genetic variation are the substrate of evolution, and it is essential to consider their role and preservation under non-pathological conditions too. Although mutations play a key role in cancer, a"mutator phenotype" itself does not seem sufficient to lead to carcinogenesis and metastasis in most scenarios. Mathematical models and other computational tools have become an essential weapon in describing the evolutionary dynamics of cancer, from agent-based models to partial differential equations and systems biology. Assessing how chromosomal alterations, gene regulatory networks, epigenetic modifications and their timing influence the fitness, robustness and phenotypic plasticity of tumour cells is essential to see the full picture in cancer research.

LOW DIMENSIONALITY OF PHENOTYPIC SPACE AS AN EMERGENT PROPERTY OF NETWORK TOPOLOGY

Pradyumna Vinod Harlapur (Department of Bioengineering, Indian Institute of Science, Bengaluru, India)

Cell fate determination is governed by complex regulatory networks formed by gene interactions. Despite the complexity of their dynamics, these gene regulatory networks (GRNs) constrain the potential phenotypic outcomes to only the desired gene expression profiles required for the cell fates. Previously, it was found that networks driving epithelial-mesenchymal transition (EMT) are characterized by two well-coordinated "teams" of mutually antagonistic sets of nodes. One team drives the cell towards an epithelial phenotype, while the other reinforces a mesenchymal one, steering cell fate to only two possible phenotypes despite the multitude of genes governing the decision. However, the question of what design principles dictate these teams' structures, leading to the lowered dimensionality of the phenotype space observed in such networks remains unanswered. In our current investigation across diverse biological scenarios (EMT, small cell lung cancer, pluripotency, gonadal cell fate), we find a consistent pattern: these networks encompass two identifiable teams of nodes steering mutually exclusive phenotypes, demonstrating a reduction in the phenotypic space. Moreover,

higher team strength is associated with reduced complexity within the emergent phenotypic space. Our analysis shows how the coordinated and coherent topological interaction between genes regulates the phenotype space and can help understand the reasons for heterogeneity observed in various contexts in cancer.

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4 STATES ≠ 4 DIMENSIONS: PRONEURAL - MESENCHYMAL ANTAGONISM DOMINATES THE PATTERNS OF PHENOTYPIC HETEROGENEITY IN GLIOBLASTOMA

Harshavardhan BV (IISc Mathematics Initiative, Indian Institute of Science, India)

The aggressive nature of glioblastoma (GBM) – one of the deadliest forms of brain tumours – is majorly attributed to underlying phenotypic heterogeneity. Early attempts to classify this heterogeneity at a transcriptomic level in TCGA GBM cohort proposed the existence of four distinct molecular subtypes: Proneural, Neural, Classical and Mesenchymal. Further, a single-cell RNA-seq analysis of primary tumours also reported similar 4 subtypes mimicking neuro-developmental lineages. However, it remains unclear whether these 4 subtypes identified via bulk and single-cell transcriptomics are mutually exclusive or not. Here, we perform pair-wise correlations among individual genes and gene signatures corresponding to these proposed subtypes, and show that the subtypes are not distinctly mutually antagonistic in either TCGA or single-cell RNA-sequencing data. We observed that the proneural (or neural progenitor-like) – mesenchymal axis is the most prominent antagonistic pair, with the other two subtypes lying on this spectrum. These results are reinforced through a meta-analysis of over 100 single-cell and bulk transcriptomic datasets as well as in terms of functional association with metabolic switching, cell cycle and immune evasion pathways. Finally, this proneural-mesenchymal antagonistic trends percolate to the association of relevant transcription factors with patient survival. These results suggest rethinking GBM phenotypic characterization for more effective therapeutic targeting efforts.

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CHROMOSOMAL INSTABILITY AS A SOURCE OF PHENOTYPIC VARIATION IN CHILDHOOD B-ACUTE LYMPHOBLASTIC LEUKEMIA

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Other authors: Óscar Molina, Gabriel Fernández Calvo, Víctor M. Pérez García, Pablo Menéndez.

Aneuploidy, characterised by an abnormal number of chromosome copies, impacts approximately 80% of tumours. Chromosomal instability (CIN) leads to abnormal mitosis, resulting in an aneuploid karyotype. Although karyotype alterations have long been used for patient classification, identifying high-risk patients remains a significant challenge in childhood B-acute lymphoblastic leukemia. We have introduced a heterogeneity index, relying on ecological and statistical measures, capable of classifying patients in our cohort based on their aneuploidy state. Additionally, we've developed a computational framework to explore the role of CIN in childhood B-ALL. Our findings suggest that a low-intermediate level of CIN is optimal for tumour cells, generating diversity without compromising cell viability significantly. In our agent-based model, we assumed random chromosome segregation (all chromosomes with an equal probability of missegregation), with selection occurring afterward. As our experimental data revealed preferential gains or losses of certain chromosomes, we curated the Mitelman database of chromosome aberrations and gene fusions in cancer to identify these frequencies. We classified chromosomes as loss-positively-selected, gain-positively-selected, or neutral, validating this classification in a local cohort. Subsequently, we are examining the cell processes allocated to each group based on bulk-RNA-seq data from our patient cohort. The tight link between aneuploidy state, chromosomal instability, and prognosis in childhood B-ALL underscores the importance of identifying processes benefiting from their action, paving the way for new therapeutic approaches.

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MATHEMATICAL MODELS OF CANCER IMMUNOTHERAPY

Juan Belmonte Beitia, Álvaro Martínez Rubio

This session encompasses topics related to mathematical approaches of cancer immunotherapy to gain biological and medical understanding or to explain biological phenomena of the immunotherapy in tumors.

We will focus our attention on mathematical modeling and applications in different treatments with immunotherapy alone, or combinated with chemo and radiotherapy. The immunotherapy treatment ranges from CAR-T cells therapy, oncolytic virus, stimulation of the immune system, etc.

Mathematical approaches including analytical and computational results will be appropriate.

COMPUTATIONAL MODELLING OF CAR-T THERAPY: FROM PHARMACOKINETIC DESCRIPTION TO PATIENT-LEVEL PREDICTIONS

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Other authors: C. Prats, G. Calvo-Rojas, D. López-Codina, E. Olesti.

Over the past decade, chimeric antigen receptor (CAR) T-cells have achieved remarkable success against several haematological malignancies, leading to the approval of various pharmaceutical CAR- T products. Despite initial success of some anti-CD19 and BCMA products, a substantial fraction of patients initially experiencing remission still encounter relapse within a year due to multiple factors [1]. Understanding the complex cellular dynamics arising from CAR-T therapy can provide insights into how this treatment might be best implemented to improve cancer therapy. In contrast to traditional chemotherapy, characterised by predictable dose-exposure relationships resulting from the well-understood processes of absorption, distribution, and elimination of chemical molecules, CAR-T pharmacokinetics are highly heterogeneous hindering the establishment of reliable therapeutic windows [3]. Since the approval of the first product, several CAR T-cell kinetics models have already been published [2]. This work reviews the most significant models available in the present literature, as well as other bibliography with relevant applications for CAR-T therapies across the fields of mathematical biology, pharmacology and immunology. This revision offers a comprehensive framework through which to understand and implement CAR-T models based on: 1) the biological actors

that these might capture, 2) the mathematical tools available to represent such biological constituents, and 3) the frameworks through which such models might be implemented based on the information available from reality. Beyond serving as a resource that consolidates current CAR-T mathematical modelling knowledge during these early stages of the discipline, this work seeks to serve as a platform to foster communi- cation and comprehension across biomedical researchers and modellers. Such a collaborative effort is fundamental in order to facilitate the often-challenging task of bringing modelling closer to the clinic.

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CAR-T CELL IMMUNOTHERAPY: FROM THE BENCH TO MATHEMATICAL MODELING

Luciana Rodrigues Carvalho Barros (Center for Translational Research in Oncology, Instituto do Câncer do Estado de São Paulo, Fundação Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brasil)

CAR-T cell immunotherapy is revolutionizing treatment for hematological malignancies. Proof-of-concept experiments were made in preclinical mouse models before the clinical trials. Our and other groups showed that less in vitro expansion time could bring benefits decreasing exhaustion and increasing CAR-T cell memory formation. Then we develop CARTmath, a software to make in silico experiments of mouse models. Based on clinical trial data we developed a multiphasic model of CAR-T cell therapy including several phenotypes of CAR-T cells: effector, memory, and exhaustion. With the higher availability of CAR-T cell therapy, many resistance mechanisms emerged. We continued to develop models and now included resistant tumor cells, trying to predict antigen-positive or negative relapses.

UNDERSTANDING THE ROLE OF B CELLS IN THE TREATMENT WITH CAR-T CELLS FOR ACUTE LYMPHOBLASTIC LEUKAEMIA

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Chimeric Antigen Receptor T (CAR-T) cell therapy has been proven to be successful against different leukaemias and lymphomas. This presentation shows an analytical and numerical study of a mathematical model describing the competition of CAR- T, leukaemias tumor and B cells. The model is formulated and its basic properties are determined. Of great importance is the relapse of tumor cells and we detail this fact in the presentation. Finally, we make a sensibility analysis in order to gain insights on the most relevant parameters of the model. We discuss these results in the light of the available evidence.

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MODELING CD19 RELAPSES AFTER CAR-T CELL THERAPY IN B CELL LEUKEMIA: INSIGHTS AND IMPLICATIONS

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Other authors: Á. Martínez-Rubio, A. Niño-López, M. Rosa

This work introduces a mathematical model to analyse CD19-relapses post chimeric antigen receptor (CAR) T cell therapy in B cell acute lymphoblastic leukemia (B-ALL), a prevalent pediatric leukemia. Despite the promising response rates of CAR T cell therapy targeting CD19+ leukemic cells [1,2] and T-cell leukemias [3], a notable fraction of patients experience relapse. The model, constructed using partial differential equations, considers diverse scenarios of CAR T cell therapy and delves into the emergence of CD19-relapses, wherein leukemic cells undergo CD19 antigen loss and persist in proliferation. By considering factors like CAR T cell dynamics, CD19 expression levels, and cellular interactions, the model offers insights into potential mechanisms governing treatment resistance and relapse phenomena. It not only aids in understanding the interplay between CAR T cells and leukemic populations, but also informs therapeutic strategies to counter CD19-relapses. Moreover, the model's flexibility enables its extension to explore analogous dynamics in other hematological malignancies and

immunotherapeutic interventions, thus providing a deeper comprehension of treatment outcomes and guiding the development of more effective therapies.

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INDIVIDUAL PATIENT DYNAMICS OF CAR T-CELL THERAPY IN LYMPHOMA: MODEL SELECTION AND RESPONSE PREDICTION

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Other authors: M. Rosa, F. Locke, A. Traulsen, P. Altrock

Most of the mathematical works on CAR T-cell therapy focus leukaemia, while a minority have explicitly considered lymphoma. This is notable considering that CAR T-cell therapy has been as successful, and the prognosis for relapse patients with lymphoma is even more challenging than that for B-ALL. One of the reasons is the higher complexity of the malignancy, which is not restricted to the circulatory system and shares characteristics with solid tumours. This implies that the role of the microenvironment is likely to be more decisive. In this work we use a previously published framework for Non-Hodgkin Lymphoma [1] to leverage data from 21 adult patients from the phase 2 clinical trial for Axicabtagene Ciloleucel, the approved anti-CD19 CAR product [2]. We fit two models with different terms for CAR T-cell expansion: One depends on the tumor cell concentration and the other on the interaction with the hosts T-cells. We employ the optimal model to study the association between parameters and clinical measures of response. Finally, we used model-based simulations to find biomarkers and test hypothesis regarding the dynamics of the response.

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https://doi.org/10.1056/NEJMoa1707447

T CELL-CANCER CELL CONJUGATE DYNAMICS IMPACT TIME TO EQUILIBRIUM OR CANCER EXTINCTION

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Cancer is a complex, often tissue-specific disease that can lead to neoplastic outgrowth hallmarked by genetic, epigenetic, and microenvironmental factors. Adaptive tumor suppression involves the immune system, which can target pre-cancerous and cancerous cells and induce cell death. Compared to chemotherapy and radiotherapy, cellular immunotherapies modify immune cells to induce the killing of tumor cells. These processes are effective due to the direct killing of target cancer cells, such as stimulated and selected or engineered T lymphocytes. We investigate the processes of T cell conjugation and killing in T cell-target cancer cell engagement. To this end, we focus on the dynamic role of the T cell-cancer cell conjugation in small and large populations, by applying stochastic and deterministic dynamic systems approaches. We question the assumption that the conjugate dynamic is in a quasi-steady state. With this assumption, tumor and T cells can reach a stable coexistence state. Dropping this assumption leads to the elevated possibility of tumors escaping from immune surveillance, slower convergence to tumor-immune cell co-existence, and faster tumor extinction. We conclude that T cell-cancer cell conjugate dynamics could play an important role in the evasion of immune surveillance and cellular immunotherapy.

UNRAVELLING BRAIN PHYSIOLOGY AND PATHOLOGY: THE ROLE OF MATHEMATICAL MODELLING

Chiara Giverso, Giulio Lucci

Understanding the intricate mechanisms that regulate brain physiology and pathology is crucial for the development of effective treatments for serious diseases, such as brain tumours and neurodegenerative disorders. In this context, alongside biological and clinical investigations, mathematical models can provide powerful tools for accelerating the process of exploring brain function by providing frameworks capable of simulating the fundamental aspects of the brain at scales from individual neurons to the whole organ. The aim of this mini-symposium is to bring together researchers working on the mathematical modelling of the brain in both physiological and pathological conditions, at both cellular and tissue scales, to discuss recent advances in the field. Specific topics of the mini-symposium will include, but are not limited to: modelling of brain tumour growth, with particular emphasis on metastasis formation, phenotypic switching, therapeutic treatments, and cell metabolism; physiology and pathology of axonal growth, with emphasis on mechanics as a key feature for understanding neural development and neurodegenerative diseases. The mini-symposium will also provide an opportunity to foster discussion and collaborations among researchers interested in brain modelling, thereby promoting the development of new mathematical tools capable of describing brain function and dysfunction.

INCORPORATING PHENOTYPIC HETEROGENEITY IN MATHEMATICAL MODELS FOR THE GROWTH OF BRAIN TUMOURS: A NON-LOCAL REACTION-DIFFUSION APPROACH

Francesca Ballatore (Department of Mathematical Sciences, Politecnico di Torino)

In recent years, there has been an increasing application of mathematical models, specifically reaction-diffusion equations with non-local terms, to advance our theoretical understanding of the intricate mechanisms governing the spatial spread and phenotypic evolution of populations characterized by a continuous trait [1, 2]. Our model is conceived as a reaction–diffusion partial integro-differential equation (PIDE), providing insights into the dynamics of a growing tumour, characterized by cells with different proliferative capabilities. Within this framework, the phenotypic state of each individual is characterized by a continuous structuring variable. The equation for the growing tumour population is complemented by a reaction-diffusion equation regulating the concentration of oxygen, useful for cell proliferation. The model incorporates spatial anisotropy of the extracellular environment, through anisotropic diffusion tensors, into

both equations. Through numerical simulation and asymptotic analysis, we explore traveling-wave solutions and find that incorporating phenotypic heterogeneity results in a complex wave profile, emphasizing the dominance of cells in different phenotypic states at distinct spatial positions within the advancing wave. Furthermore, three-dimensional numerical simulations are conducted to analyze the evolution of brain tumours within a three-dimensional brain geometry reconstructed from magnetic resonance images, taking into account patient-specific data on oxygen diffusion and cell-biased motion along the preferential directions of white matter tracts derived from diffusion tensor imaging (DTI) data.

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MODELING THE GROWTH OF BRAIN METASTASES

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Brain metastases (BMs) are a major clinical problem, as they represent the most common intracranial tumors in adults. These tumors are caused by single tumor cells or groups of cells that detach from the primary site and migrate to the brain, where they give rise to clusters of metastatic cells that grow and form macrometastases.

Understanding the underlying mechanisms of BM formation is crucial for the development of effective therapeutic strategies. To shed light on this process, we have developed a discrete agent-based model (ABM). Our ABM is based on a fixed vasculature and cells that are characterized by a continuous phenotype variable. In this model, cells can proliferate, migrate, undergo cell death, or become quiescent, resulting in the emergence of complex phenomena and the formation of large metastases.

By employing this ABM approach, we have established a quantitative in silico framework that could serve as a powerful tool for preclinical studies. Despite its simplifications, our model has demonstrated its effectiveness by successfully replicating experimental data obtained from animal studies.

THE MULTISCALE MECHANICS OF AXONAL GROWTH

Giulio Lucci (Politecnico di Torino)

Axons, the slender protrusions of neurons, exhibit remarkable mechanical sensitivity. Indeed, their surrounding cortex can actively contract in both the direction along the axon (axial) and around its circumference (hoop) in response to externally applied deformations or drug-induced structural alterations. However, the precise mechanisms coordinating these axial and circumferential contractions, as well as their important coupling, remain unclear. We address this gap by developing a mathematical model for axon mechanics based on the active strain theory. We treat the axon as a continuous elastic body with a passive inner core (cytoplasm) and an outer layer capable of active contractions in the hoop and axial directions. Evolution equations for these active strains are derived, and our approach reveals the inherent coupling between active contractions via the Mandel stress tensor. After a qualitative analysis, we discuss the model's numerical implementation and compare simulation results with experimental data. These comparisons show a very good agreement, particularly regarding changes in axonal diameter due to drug treatments or uniaxial stretching.

SPATIAL MULTI-SCALE MODEL OF TUMOR METABOLISM

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In this work, a model of tumor metabolism highlighting the spatiotemporal heterogeneity is developed. This model makes it possible to test different scenarios of environmental stress and to assess their consequences on the metabolic trajectory of individual cells as well as of the tissue as a whole. Moreover, by combining continuous and discrete approaches within a hybrid multiscale model, cell metabolism is spatially contextualized and complex behaviors emerge. The model calibrated with data from glioma cells highlights some therapeutic consequences.

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TOPOLOGICAL DATA ANALYSIS FOR APPLICATIONS IN BIOMEDICINE

Salvador Chulián García, Bernadette Jana Stolz-Pretzer

Topological data analysis (TDA) has emerged as a powerful framework combining mathematics and computation for understanding complex datasets, with many recent successes in biomedicine. Methods in TDA are derived from concepts in algebraic topology to analyze and interpret shape in high-dimensional data via geometric and topological properties. TDA combines a variety of techniques that allow insights into underlying shape across multiple scales, patterns of spatial organization, and multispecies relationships in biological systems. In particular, TDA has proven transformative in allowing researchers to quantify the complexities of biological phenomena providing a unique lens through which to explore the fundamental principles governing biological systems.

Throughout this minisymposium, four distinct talks will explore several aspects of TDA and its applications in biology, showcasing its versatility and relevance in contemporary research. These talks will emphasize the practical use of TDA in addressing biological questions while also elucidating some of the theoretical foundations. The presentations will cover a spectrum of topics ranging from the analysis of multi-species localization patterns within tissues to the modeling of periodic biological processes using persistent cohomology. The symposium will further explore the development of novel topological descriptors to capture spatial patterns in the tumor microenvironment, as well as present innovative TDA pipelines for the multi-localization of different cell types within complex spatial domains.

MODELLING PERIODIC BIOLOGICAL PROCESSES AS PERSISTENT COHOMOLOGY CLASSES

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Other authors: M. Youssef

Topological data analysis is a computational framework designed for estimating and analysing the topology of point clouds. Starting in the early 2000s mathematicians have been translating the theory of algebraic topology into widely applicable algorithms. On the biological side, single-cell data experiments provide a point cloud whose points are cells and dimensions are genes. The coordinates of the points correspond to estimates of RNA levels of each gene in each cell at the time that the tissue is collected.

Since single-cell experiments can only capture gene expression data at a given time, reconstructing the dynamic expression patterns is a difficult proposition. A recurring theme is

to treat the single-cell experiment as a sample of the underlying phase space of all possible RNA expression levels. The overarching vision in this paradigm is to associate the geometric and topological features of this sampled phase space with their underlying dynamical biological processes.

The focus of this work is to reconcile the persistent cohomology groups in dimension one with underlying biological processes, with the premise that there exist generators of this cohomology group that correspond to periodic biological processes. Persistent cohomology provides us with a purely geometric brute-force method to identify subsets of genes that are likely producing periodic processes. We then employ the persistent cohomology-based circular coordinates of De Silva [1] and define a 1-form-based generalisation of Barynsikov's lead-lag analysis [2] to quantify the role of specific genes and estimate their ordering in the periodic process.

As a proof of concept, we provide an in-depth real-world example relating a specific persistent cohomology class to the cell cycle. Further, we show how our method can be used as an exploratory tool to generate hypotheses about novel types of periodic processes in biology.

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CAPTURING SPATIAL PATTERNS WITH TOPOLOGICAL METHODS

Ondrej Draganov (ISTA (Institute of Science and Technology Austria))

Given a collection of cells of various biological types with known spatial coordinates, how can we quantitively describe their intertwined spatial arrangements? Can certain spatial patterns in the tumor microenvironment be algorithmically summarised? We will present a new topological descriptor that can be used to extract spatial features from such systems. The method builds on techniques from the mathematical field of topological data analysis.

CHROMATIC COMPLEXES FOR SPATIAL BIOLOGY: COMPUTATIONAL ASPECTS

Abhinav Natarajan; Maria Jose Jimenez (University of Oxford, United Kingdom; Universidad de Sevilla, Spain)
Other authors: Thomas Chaplin

The chromatic alpha filtration [1] is a generalization of the alpha filtration that can encode spatial relationships among classes of labelled point cloud data, and has applications in topological data analysis of multi-species data. To speed up computations, we introduce the chromatic Delaunay-Čech and chromatic Delaunay-Rips filtrations [2]. Using tools from discrete Morse theory, we show that the chromatic Delaunay-Čech and chromatic alpha filtrations capture the same topological information. We also show that our constructions are stable to perturbations of the data in a suitable sense. Finally, we demonstrate the computational speedup obtained using our constructions with numerical experiments. Our results justify the use of chromatic Delaunay-Čech and chromatic Delaunay-Rips filtrations in applications.

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RELATIONAL PERSISTENT HOMOLOGY FOR MULTISPECIES DATA WITH APPLICATION TO THE TUMOR MICROENVIRONMENT

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Keywords: persistent homology, multiplex imaging, spatial heterogeneity

State-of-the art data from multiplex immunohistochemistry images offers exquisite details on the spatial and phenotypic heterogeneity of cells in tissue samples. However, the high level of detail in these images is contrasted with a lack of methods that allow an analysis that fully exploits the available spatial information. Persistent Homology (PH) is a method from Topological Data Analysis that captures spatial information in data at multiple scales. However, PH is typically limited to the analysis of one cell type. In this talk, I will introduce two novel techniques of relational PH that capture and quantify spatial heterogeneity of multiple cell types [1]. We apply the methods to synthetic data generated by an agent-based model of tumour multiplex immunohistochemistry images [2]. We demonstrate that these techniques can predict dominant subtypes of cells and distinguish robustly between different qualitative behaviours of the model in different parameter regimes. Our methods provide a novel perspective on the spatial analysis of multiple cell types in multiplex immunohistochemistry images and overcome limits of traditional PH while being readily computable.

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MECHANISTIC LEARNING IN MATHEMATICAL ONCOLOGY

Alvaro Köhn-Luque, Saskia Haupt

There is a growing trend in developing synergistic approaches that harness the combined potential of knowledge-driven mechanistic mathematical modeling and data-driven techniques, including machine and deep learning. We refer to such hybrid approaches as mechanistic learning. The purpose of this mini-symposium is to shed light on various emerging research directions within mechanistic learning with applications to mathematical oncology.

Our objective is to illustrate that mechanistic learning, with its aim to fuse the strengths inherent in both knowledge-driven and data-driven modeling, holds substantial promise for addressing current challenges within mathematical oncology. Moreover, we aim to engage in discussions surrounding the current obstacles faced and deliberate on future research perspectives within this domain. By doing so, we aim to contribute to the enhancement of existing techniques in mathematical oncology, thereby advancing our understanding and ability to tackle the multifaceted issues in this critical field.

A REVIEW OF MECHANISTIC LEARNING IN MATHEMATICAL ONCOLOGY

Sarah Brüningk (Biomedical Data Science Lab, ETH Zurich, Switzerland)
Other authors: S. Haupt, J. Metzcar, C. R. Jutzeler, P. Macklin, A. Köhn-Luque, S. C. Brüningk

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Mechanistic learning, the synergistic combination of knowledge-driven and data-driven modeling, is an emerging field. In particular, in mathematical oncology, the use of mechanistic learning is growing. This introductory talk of this mini-symposium aims to capture the current state of the field and provide a perspective on how mechanistic learning may further progress in mathematical oncology. We highlight the synergistic potential of knowledge-driven mechanistic mathematical modeling and data-driven modeling, such as machine and deep learning. We point out similarities and differences regarding model complexity, data requirements, outputs generated, and interpretability of the algorithms and their results. Following our recent review [1], we organize combinations of knowledge- and data-driven modeling into four categories (sequential, parallel, intrinsic, and extrinsic mechanistic learning) and summarize a variety of approaches at the interface between purely data- and knowledge-driven models. Using examples predominantly from oncology, we highlight a range of techniques including physics-informed neural networks, surrogate model learning, and digital twins and shortly map the subsequent

talks to these categories.

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HOW TO MAKE CLINICAL PREDICTIONS WHEN WE DO NOT KNOW EVERYTHING?

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In clinical practice, a plethora of examinations is conducted to assess the state of a certain pathology. These span from blood sample analysis, clinical imaging (e.g. CT, MRI) and biopsy sampling are among the most important diagnostic and prognostic tools. Such medical data correspond to snapshots in time of the patient's state, since current standard of care (SoC) is not based on emergent technologies of real-time measurements, such as liquid biopsies or biosensors. Moreover, clinical data refer to different biological scales since imaging, such as MRI, typically provides an organ level picture of a disease (macroscopic), biopsies represent cellular patterns at a tissue (mesoscopic) level and -omics, FACS or molecular markers allow for sub-cellular insights. Finally, the biophysical mechanisms that regulate phenomena in all these scales are not completely known. Therefore, current clinical care faces the following challenges: (C1) data collection is sparse in time since it relies on patient's clinical presentation, (C2) we lack the knowledge/uncertainty of the mechanisms involved in regulating these data variables across different scales (structural uncertainty), and (C3) medical data are multiscale. Therefore, integrating these data to predict the future of a disease and propose an appropriate treatment is a formidable task.

I propose to harness the ability of mechanistic models to integrating the existing biological knowledge and deal with the emerging dynamics. At the same time complete the missing knowledge by using data intensive techniques. Here I will present (i) a Bayesian regression framework of combining models and machine learning to predict tumor growth and (ii) model-driven classification method to assess the graft loss risk in kidney transplantation patients.

PREDICTING ANATOMICAL TUMOR GROWTH IN PEDIATRIC GLIOMA BY GUIDED DENOISING DIFFUSION MODELS

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Other authors: D. Laslo, M. Monzon, D. Ramakrishnan, M. von Reppert, S. Stoller, A. S. Guerreiro Stücklin, N. U. Gerber, A. Rauschecker, J. Nazarian, S. Mueller, C. Jutzeler

Pediatric diffuse midline glioma (DMG) is a rare and challenging brain malignancy located in sensitive brain regions hindering surgical resection. Radiotherapy remains the only life-prolonging treatment for DMGs. Response could likely be improved by personalized geometric dose distributions informed by anatomical tumor growth predictions. This feasibility study demonstrates a combination of mechanistic modeling of tumor size with a data-driven image-to-image translation task. Based on adult glioblastoma and pediatric DMG MR imaging cohorts from the 2023 Brain Tumor Segmentation Challenge, we trained a guided denoising diffusion implicit model (DDIM) to generate images of enlarged tumors while maintaining the surrounding brain anatomy. Test set performance was evaluated using the Frechet Inception Distance (FID), and Structural Similarity Index (SSIM). Qualitative evaluation involved visual classification of real vs generated images by human observers. The optimized network was tested to forecast anatomical tumor growth in five DMG patients from an independent dataset comprising longitudinal T2-FLAIR images for which a simple ODE-model was used to describe tumor growth to provide target sizes. We obtain high-fidelity generated images, supported by an FID of 12.4 and 0.8 SSIM on the adult test set. Despite the smaller pediatric dataset yielding a 34.8 FID and 0.84 SSIM, expert radiologists failed to distinguish generated from real MRIs (mean recall and precision of 0.51). The generated anatomical predictions also closely resemble the observed tumor progression in the longitudinal pediatric DMG subset. Notably, the direction and extent of tumor growth align while the anatomy of the brain slice is preserved, yielding a mean DICE score of 0.8 between predicted and true tumor growth. In summary we present a promising sequential combination of mechanistic and purely data driven approaches to enable personalized anatomical tumor growth predictions on imaging data over time.

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MECHANISTIC LEARNING FOR METASTASIS MODELING, UNDERSTANDING AND PREDICTION

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In the majority of solid cancers, secondary tumors (metastases) are the main cause of death. Quantitative mathematical modeling could be valuable in testing biological theories against empirical data, bringing mechanistic insights, and designing numerical tools predictive of metastatic relapse or the impact of therapies. I will present recent results from COMPO (COMPutational pharmacology and clinical Oncology) aiming at combining mechanistic modeling and machine learning ("mechanistic learning"). The general framework is based on a

physiologically-structured partial differential equation for the time dynamics of a population of metastases. I will present results on the modeling of neoadjuvant treatment in a pre-clinical model of breast cancer to formulate and test mechanistic hypotheses about differential effects on primary versus secondary disease, evaluate the impact of biomarkers on metastatic development, and investigate the impact of modulating the dosing regimen. Then, I'll discuss two clinical applications: brain metastasis from non-small cell lung cancer, where we compare models relying on different biological hypotheses about dissemination and growth, and metastatic relapse in early-stage breast cancer, where we used a combination of machine learning techniques and mixed-effects statistical modeling methods to individualize predictions of the model parameters from data available at diagnosis allowing patient-specific prediction of the time to metastatic relapse. Together, these results represent a step towards integrating mathematical modeling as a predictive tool for personalized oncology.

PATIENT-SPECIFIC FORECASTING OF PROSTATE CANCER GROWTH AND RADIOTHERAPY RESPONSE USING BIOMECHANISTIC MODELS AND HYBRID CLASSIFIERS

Guillermo Lorenzo (Health Research Institute of Santiago de Compostela, Spain and Oden Institute for Computational Engineering and Sciences, The University of Texas at Austin, USA)

The current clinical protocols to manage prostate cancer (PCa) enable the detection and successful treatment of these tumors at an early stage. However, recent studies suggest that many PCa patients are being overtreated, and hence prone to potential treatment side-effects (e.g., incontinence, impotence) that can adversely impact their quality of life without improving longevity. Furthermore, undertreatment of PCa is another important clinical challenge, as it may lead to rapid growth of aggressive tumors, treatment failure, and reduced survival. The overtreatment and undertreatment of PCa have the same origin: the limited individualization and observational nature of the clinical management of these tumors. In this talk, I propose to address these critical, unresolved issues by using patient-specific forecasts of PCa growth and treatment response, along with hybrid classifiers that take biomechanistic inputs to predict the occurrence of clinical events of interest. I will present the application of this predictive framework in two scenarios where longitudinal data are collected as part of the standard-of-care management of PCa: active surveillance of lower-risk tumors before primary treatment, and the post-treatment monitoring of patients after radiotherapy. For each application, I will show how a biomechanistic model can be built, calibrated, and validated to obtain personalized predictions of tumor growth and therapeutic response. Then, logistic classifiers will be trained with biomechanistic model outputs to identify tumors progressing towards higher-risk disease during active surveillance or developing a recurrence after radiotherapy. Finally, although further development and validation over larger cohorts are needed, I will posit that the technologies presented in this talk can contribute to advance the observational, population-based standards in clinical oncology towards a predictive, personalized paradigm.

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ON THE USE OF NEURAL NETWORKS FOR PARAMETER IDENTIFICATION IN MATHEMATICAL MODELS OF GLIOBLASTOMA EVOLUTION.

Marina Pérez-Aliacar (Aragón Institute of Engineering Research (I3A), University of Zaragoza)
Other authors: M. Tambo, J. Ayensa-Jiménez, M. Doblaré

Glioblastoma (GBM) is the most common and lethal brain cancer, with a median survival of only 14 months after diagnosis. It is an extremely heterogeneous tumor, which represents a challenge in the design of effective therapies. Indeed, despite considerable effort, GBM remains largely resistant to treatment [1]. Mathematical models have proven useful to gain insights into GBM evolution and to predict its response to therapy. However, population-level data, widely used to fit these models, does not yield accurate predictions for individual patients due to the aforementioned inter-tumor heterogeneity. Thus, in the race for developing successful treatments, patient-specific models play a key role [2]. The design of such personalized models requires to integrate patient-specific information to calibrate them, and parameter estimation becomes a key issue. It has usually been carried out via standard minimization procedures, such as the Levenberg-Marquardt algorithm, which are very computationally expensive, especially when working with patient-specific models, and sometimes lack robustness. The use of machine learning, in particular of Deep Neural Networks (DNNs), has been proposed as an alternative for parameter identification, allowing to work with reduced order models that can be evaluated in real time [3]. This is particularly relevant for the use of mathematical models as support tools for clinicians, allowing them to promptly obtain personalized information about the patient. In this work, we explore the use of DNNs to estimate, from in vitro images of GBM cells, the most relevant parameters in two different models of GBM evolution, a continuum and an agent-based model. Both models have advantages and disadvantages for studying tumor evolution, and we believe it is the combination of both which allows the most fruitful analysis. Hence, we also exploit the DNN approach to establish equivalences among the parameters of both models, bridging the gap between them.

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AUGMENTING MECHANISTIC MODELS WITH MACHINE LEARNING TO PREDICT CANCER TREATMENT OUTCOMES

Alvaro Köhn-Luque (Oslo Centre for Biostatistics and Epidemiology, Faculty of Medicine, University of Oslo, Oslo, Norway and Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Oslo, Norway)
Other authors: L. Schmiester, A. Kielland, E. M. Myklebust, K. Leder, J. Foo, A. Frigessi

In the era of data-driven breakthroughs powered by machine learning, we are witnessing remarkable successes in fields rich with data, such as imaging sciences, protein structure analysis, and language processing. Concurrently, mechanistic modeling, which involves crafting equations to represent well-understood system mechanisms, continues to impact multiple areas. Yet, many real-world scenarios fall somewhere between these two paradigms. Clinical oncology, in particular, often faces limited or imperfect knowledge of the underlying mechanisms alongside sparse and noisy data. In this context, modeling is required to provide decision support to enhance personalized diagnosis and prognosis for cancer patients. This talk explores the potential synergy between mechanistic modeling and machine learning, aiming to harness the strengths of both approaches while mitigating their respective limitations. I will illustrate this concept through two ongoing projects. Firstly, I will discuss efforts to design a gene-expression biomarker for treatment response in breast cancer patients. This is done using statistical models to learn the residuals left by a mechanistic model. Secondly, I will delve into predicting disease progression in multiple myeloma patients using longitudinal measurements of cancer burden together with patients' clinical characteristics. In this case, we combined mechanistic and machine learning models through a hierarchical Bayesian approach. The ultimate goal of augmenting mechanistic modeling with machine learning is to empower clinicians with robust tools to assess the efficacy of novel cancer treatments and enhance patient care.

COMPLEXITY SCIENCE FOR BIOLOGICAL AND MEDICAL PROBLEMS

Jesús J. Bosque

By their very nature, Complexity Science and Mathematical Biology are two closely related disciplines. Despite the proximity between the two in terms of goals and tools, Complexity Science is usually underrepresented within Mathematical Biology conferences.

In broad terms, Complexity Science uses mathematical models to describe systems made up of multiple components with the ambition of understanding global phenomena emerging from low-level interactions. The generality of this concept, together with the power of insightful mathematical tools and increasingly available data have led to a plethora of applications. Specifically within Biology and Medicine, Complexity Science has brought relevant scientific advances, from unraveling intricate networks of gene interactions to representing diseases as a landscape of interdependent alterations.

Remarkably, all progresses made in those directions are deeply rooted in mathematical techniques and quantitative analyses. Therefore, scientists from Mathematical Biology and Complexity Science must join forces to produce breakthrough findings that impact Biology and Medicine.

In this mini-symposium, we bring together four researchers of diverse geographical and scientific backgrounds whose research is rooted in Complexity Science. They will cover diverse applications across multiple areas of Biology and Medicine, all of which are of interest to the broad community of Mathematical Biologists. The topics presented here span four different scales of life, starting from the mitochondria and continuing with assemblies of neurons, to later on tackling the mortality of individuals and finishing with drug repurposing at inter-disease populations.

We trust that this mini-symposium will catch the interest of Mathematical Biologists with a diverse set of topics that lay within their field but are not traditionally covered in these conferences.

DATA-DRIVEN APPROACHES TO STUDY THE COMPLEXITY OF ORGANELLES

Konstantinos Giannakis (Department of Mathematics, University of Bergen)
Other authors: I.G. Johnston

Mitochondria are the indispensable power source of eukaryotic cells, which in turn contain dynamic populations of these morphologically and genetically diverse organelles that replicate,

die, and interact almost like social entities. This talk will revolve around two complex and scientifically challenging aspects of organellar biology. Focusing on plant mitochondria (mt) and their idiosyncrasies (ie, they are fragmented and mobile, each possess a fraction of the whole gene set and their encounter networks can be modeled as graphs), our group and collaborators built upon previous research on the social aspect of their encounter networks. Inspired by previous work on the influence of mitochondrial dynamics on genetic dynamics, we asked if these complex and far from random networking structures can allow the emergence of a complete mt genome. We discovered that this corresponds to an instance of the well-known coupon collector's problem, and we showed that these encounter patterns can indeed allow the emergence of the whole mt genome, which is attributed to the complex degree distribution of these networks [1]. Tracing the evolution of these organelles, we know they have lost parts of the original set of gene sets. Different evolutionary hypotheses (or a combination of them!) have already been proposed as potential candidates that triggered or catalyzed this gene retention/loss trajectories [2]. Recently, we investigated another complex aspect of organelle genome evolution: the potential correlation between ecological and lifestyle traits (like parasitism, habitat, etc) with the different gene retention patterns we observe across the tree of life. We provide statistical support on some relationships, opening directions for further research on the complex interplay between traits and organellar gene evolution [3]. We finally asked the same questions on another vital organelle found in plants, the plastid.

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USING NEURONAL CULTURES AS A MODEL SYSTEM FOR MEDICINE: FROM COMPLEX NETWORKS TO THERAPY

Jordi Soriano (Departament de Física de la Matèria Condensada, Universitat de Barcelona
Universitat de Barcelona Institute of Complex Systems (UBICS))

Biological neurons grown in the laboratory in the form of neuronal cultures are one of the most compelling examples of a complex system, in which an ensemble of initially disconnected neurons is able to reconnect and form a de novo network within days. By using resources from neuroengineering, one can coarsely control this connectivity and build in vitro systems that mimic key organizational features of the brain, specifically modularity. Such systems are useful to design brain-on-chip models to explore and treat neurological disorders in a controlled manner. In this talk, I will show different examples of how innovative experiments in neuronal cultures, in combination with graph theory, have help to model different pathologies in vitro

and in silico, including Huntington's, Alzheimer's, and Parkinson's. For the latter, I will also show how in vitro approaches using human induced pluripotent stem cells (hIPSCs) have revolutionized our capacity to understand the disease and advance towards applicable therapies.

BRIDGING NETWORKS FOR DRUG REPURPOSING: INSIGHTS FROM NETWORK MEDICINE

Lucía Prieto Santamaría (E.T.S de Ingenieros Informáticos,
Universidad Politécnica de Madrid)

Network medicine (NM) studies disease through the lens of network science. NM has been key to numerous applications, ranging from disease classification and progression, to finding better treatments. In this direction, NM has proposed a number of frameworks that are able to identify hypotheses for drug repurposing, i.e. the strategy of finding new uses for already existing drugs that were originally developed for other diseases. Drug repurposing bypasses some of the steps in the drug development process, what reduces several of the risks, financial and time costs associated with de novo drug discovery.

NM uses varied biomedical data structured in the form of graphs with the aim of prioritizing repurposing opportunities. In this context, and based on the foundations of the Human Disease Network (HDN), DISNET platform collects biomedical information from several public sources and integrates it into a heterogeneous network whose nodes are diseases. Other node types may include symptoms, genes, proteins, and drugs. The links of the network represent the connection between diseases and genes, diseases and drugs, interactions between proteins, and the interactions between drugs, among others.

With this network, we have presented a set of complementary methodologies towards suggesting drug repurposing candidates. On the one hand, we have identified significant differences that characterize successful repurposing cases at the disease-gene connections and at the symptom similarity between diseases. On the other hand, five information paths between different node types in the network (starting from a disease, and ending on a drug) have been useful in the search for drugs to be repurposed against COVID-19. Finally, the use of Artificial Intelligence applied to these graph-structured data by means of Graph Neural Networks has also enhanced the prediction of drug repurposing candidates.

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PLANT MODELS ACROSS SCALES

Mariya Ptashnyk, Eva E. Deinum

Plants fulfill important role in terms of food security and improved environment. The typical land plants are immobile, which allows them to explore the deep soil for resources like water and nutrients. Plants are highly adaptive: they respond to their environment by continual production of new organs (roots, branches, leaves) and local adaptation of their mechanical structures. The precisely coordinated anisotropic properties of plant tissues and organs allow for the growth of large mechanically stable structures and for the long distance transport of substances. The rigid cell walls, surrounding plant cells, play a central role in every process in a plant's life not only by shaping cells and providing mechanical support, but also by presenting barriers to local transports, basis of the conduits for long distance transport, as well as protection from pathogen. The diversity and beauty of plant growth and forms has stimulated the development of new approaches to describe and model plant systems and their environment and to better understand the main mechanisms underlying plant development and growth. The objective of this symposium is to showcase recent theories and tools to describe the physics of plant growth from single cells, via development, to their interactions with the environment.

MATHEMATICAL MODELS TO UNDERSTAND ROOT-SOIL MECHANICAL INTERACTIONS

Lionel Dupuy (NEIKER, Ikerbasque, Bilbao, Spain)
Other authors: Evelyne Kolb, Jiaojiao Yao

Plant roots must overcome a range of physical obstacles to grow into the soil and capture water and mineral elements. Mechanical resistance to growth in soil is due to the radial deformation and compaction of the surrounding soil, friction at the tip of the root where the soil slips, or bending and deflection when an obstacle is impenetrable. Thanks to recent advances in live imaging, material sciences, and engineering, we now have the capability to observe root growth with great accuracy and in diverse and heterogeneous conditions. This newfound ability is revealing growth responses which current models are unable to describe. In this presentation, I will expose recent single root models proposed to describe how roots limit the energy needed to expand in soil through a control of tip shape and the location of the cell elongation, the avoidance of peak particle forces or the bypass of impenetrable obstacles. Ultimately the models proposed predict root trajectories and the overall ability of the root system to explore the soil domain efficiently.

MOBILITY OF CHARGED MOLECULES THROUGH PLASMODESMATA

Kaare H. Jensen (Department of Physics, Technical University of Denmark)
Other authors: A.H. Christensen, A. Gupta, G. Chen, H.A. Stone, W.S. Peters, M. Knoblauch

Terry and Robards have argued that the mobility of molecules through plasmodesmata is governed by their hydrodynamic radius alone [1]. However, the plasma membrane lining the cytoplasmic sleeve is presumably negatively charged. This could cause positively charged particles to be attracted to the pore boundaries, while negatively charged particles might be repelled. Such an effect could impact the mobility of molecules through plasmodesmata. To investigate this, we develop a model based on electrokinetics [2]. Our model identifies two key parameters: the interaction energy between the molecule and the pore surface, and the thickness of the electrical double layer (the Debye length) compared to the plasmodesmata aperture width. Our prediction is that the transport of molecules with the opposite charge of the pore boundary will be enhanced, while the diffusion of like-charged particles will be suppressed. We discuss the optimal conditions for this effect and re-examine the claims of Terry and Robards [1]. Finally, implications for plasmodesmata function are considered.

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ORGANIZATION OF PLANT CORTICAL MICROTUBULES ON CURVED SURFACES

Tim Tian (The University of British Columbia, Canada)
Other authors: E. Cytrynbaum, C. Macdonald

As plants develop, their shape and structure is the collective result of their individual cell's growth. The growth of each cell is, in turn, the result of subcellular processes. One such process is the formation of parallel microtubule arrays wrapping along the cell cortex. This is observed to emerge from a combination of various factors such as microtubule-microtubule interactions, nucleation, and localization of microtubule-associated proteins. Distilling this process into the interaction of one-dimensional bodies on the two-dimensional cortex, quantitative models have been proposed to emulate array formation. In particular, simulations have studied the importance of each factor in producing the ob- served order and orientation of arrays. However, most of these works make an assumption: that microtubules travel along geodesics of the cortex. Modelling microtubules as thin elastic rods constrained on a surface, it has been found that microtubule shapes resulting from curvature minimization may differ significantly from the previously assumed geodesic paths. We implement this in an agent-based, event-driven simulation.

In our preliminary work, we find that this curvature mechanics provides a strong influence for directional alignment. The resulting preferential direction competes with previously proposed mechanisms of alignment, and alludes to the presence of additional biological factors previously unaccounted for. This simulation provides the opportunity for further exploration into mechanical influences on array formation and their regulation through microtubule-associated proteins.

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EFFICIENT ALGORITHM FOR REALISTIC MICROTUBULE-BASED NUCLEATION IN THE CORTICAL MICROTUBULE ARRAY

Marco Saltini (Wageningen University & Research, The Netherlands)
Other authors: E.E. Deinum

The self-organisation of cortical microtubules in aligned arrays is a key factor in shaping the morphogenesis of plant cells and, consequently, the overall growth of the organism. Computational studies have been instrumental in revealing the factors that drive this alignment, including the topology of the simulation domain and directional imbalances among microtubule dynamic parameters. However, for over a decade, simulations aiming to realistically reproduce microtubule nucleation – i.e., the generation of new polymers, have faced significant challenges in terms of inhomogeneity of the cortical array. This issue consists of large areas of the simulation domain remaining empty of microtubules, while densely populated areas attract further nucleation sites exacerbating the inhomogeneity of the system. Here, we propose a novel, time-efficient algorithm that more realistically models microtubule nucleation. By approximating the free diffusion of nucleation sites with a likelihood of diffusion direction approach, our algorithm ensures more homogeneous arrays and a realistic nucleation mode, while avoiding the need to explicitly simulate time-consuming diffusion processes. Our approach reveals that a more accurate model of microtubule nucleation naturally leads to specific array orientations, e.g., a transverse direction in cylindrical simulation domains. With our model, we show that strong biases towards specific orientations of alignment in self-organised arrays can emerge naturally when nucleation is modelled with enhanced biological realism. Our approach opens up new avenues for quantitative comparisons of different factors influencing array orientation and, as such, can be a powerful tool for re-assessing conclusions about the drivers of microtubule alignment in plant cells.

USING 3D FINITE ELEMENT METHOD SIMULATIONS TO UNRAVEL

THE INTERPLAY BETWEEN PLANT STOMATA MORPHOLOGY AND FUNCTION

Melissa Tomkins (John Innes Centre, UK)
Other authors: C.H. Durney, M.J. Wilson, S. McGregor, J. Armand, R.S. Smith, J.E. Gray, R.J. Morris, A.J. Fleming

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Plant stomata play a crucial role in regulating gas exchange between plants and their atmosphere, thereby influencing both photosynthetic rates and the water content of plants. Despite their seemingly simple mechanical structure - a pore with a central opening that can open and close - stomata exhibit significant morphological diversity across plant species. Exploring the intricate relationship between stomatal morphology and the resulting functional diversity provides valuable insights into the evolutionary aspects of stomata. Additionally, it enables us to predict how stomata in diverse vegetation might respond to environmental changes. In this talk, I will present current models and ideas for how the interplay between geometry and material properties facilitates stomatal opening and closing. The Finite Element Method is used to simulate shape changes of different stomatal morphologies as a function of turgor pressure. Using MorphoDynamX we inflate and deflate 3D mesh representations of guard cells that are generated from confocal microscopy images. In this way we can study how different geometries determine stomatal opening and closing dynamics. Through linking function with morphology, I will address questions regarding the evolution of specific stomatal shapes. In particular, the trade-offs between response time, which is crucial for plants in rapidly changing environments, and maximum pore aperture size. Using 3D Finite Element Method simulations to unravel the interplay between plant stomata morphology and function.

[1] Woolfenden, Hugh C. et al. (2017). A computational approach for inferring the cell wall properties that govern guard cell dynamics. The Plant Journal, 92(1), 5-18. https://doi.org/10.1111/tpj.13640
[2] Carter, Ross et al. (2017). Stomatal Opening Involves Polar, Not Radial, Stiffening Of Guard Cells. Current Biology, 27(19), 2974-2983.e2. https://doi.org/10.1016/j.cub.2017.08.006
[3] Durney, Clinton H. et al. (2023). Grasses exploit geometry to achieve improved guard cell dynamics. Current Biology, 33(13), 2814-2822.e4. https://doi.org/10.1016/j.cub.2023.05.051

PLANT MORPHOGENESIS ACROSS SCALES

Antoine Fruleux (Université Paris Saclay, France)

What sets the size and form of living organisms is still, by large, an open question. During this talk, I will illustrate how we are addressing this question by examining the links between spatial scales, from subcellular to organ, both experimentally - based on live imaging and theoretically - based on stochastic PDEs describing active fluids. I will present predictions of fluctuations at multiple scales and tests of these predictions. Altogether, our results shed light on mechanisms underlying the robustness of morphogenesis.

ROOT WATER UPTAKE MODELLING ACROSS SCALES

Andrea Schnepf (Forschungszentrum Juelich GmbH, Agrosphere (IBG-3), Juelich, Germany)
Other authors: D. Leitner, J. Vanderborght

Roots help plants to take up water and nutrients from soil. Under non-stressed conditions, the transpiration demand can easily be fulfilled. However, when the soil dries out and the soil hydraulic conductivity decreases, the specific root hydraulic architecture largely determines the occurrence and level of stress. In future climates, droughts will become more likely. Mathematical models can support the development of suitable and sustainable cultivar selection and management methods under such stress conditions. We show how 3D root hydraulic architectures can be upscaled and embedded in a 1D soil model by means of a simple function with two parameters, the root system conductance and the standard uptake fraction vector. Water flow is mechanistically described as driven by potential gradients in the system and modulated by the different resistances to water flow. The 1D root hydraulic uptake model can be coupled with a model that accounts for the resistance to the radial flow in the soil volume around root segments, the so-called perirhizal zone. With this coupling, the effect of soil hydraulic properties on the root water uptake and sink terms can be accounted for. Phenomena like hydraulic redistribution and root water uptake compensation arise automatically from this mechanistically derived formulation. While other root water uptake sink functions rely on empirical factors, the parameters of the mechanistically derived functions are directly related to physical properties of the root system and of the soil and can be calculated directly from these properties. The sink term can easily be implemented in soil, crop, and land surface models for any given soil discretization specific to those models. Evaluation of the accuracy of the new 1D sink term compared to the full 3D simulation showed that it depends on the root architecture, the field spacing, and the soil type.

MODELLING THE INFLUENCE OF ROOT RHIZODEPOSITS ON SOIL HYDRAULICS AND ROOT WATER UPTAKE

Andrew Mair (NEIKER, Bilbao, Spain)
Other authors: L. Dupuy, M. Ptashnyk

Previous experimental research has found that the exudates and mucilage produced by plant roots, referred to generally as rhizodeposits, affect several soil hydraulic properties. Namely, the viscosity and surface tension of soil water, and the contact angle between menisci and the pore surface. What remains less clear though, is how these effects manifest when considering the infiltration and retention of water in the soil and the consequent impact on the availability of water for uptake by plant roots. By modifying Richards equation, we develop a novel model for soil water transport that incorporates the aforementioned influences of root rhizodeposits. The finite-element method is used to obtain numerical simulations from this model. By considering different model parametrisations, we then use our simulations to show how the various effects of root exudates and mucilage can enhance or reduce root water uptake rates, depending on the specific environmental conditions. This work suggests that the type of rhizodeposit produced by the roots of a given plant species may play a role in determining its capacity to succeed in a particular environment. Such knowledge could help identify crops that will make the most efficient use of water under a given irrigation regime or will be more resilient to certain environmental stresses.

MODELING TISSUE MECHANICS AND CELL FATE IN REGENERATION AND CANCER

Gabriel Piedrafita, Qiyao (Alice) Peng & José Manuel García Aznar

Tissue regeneration and maintenance are fundamental processes requiring a high degree of cell coordination at the tissue level. These under-explored control mechanisms are to be disrupted in cancer. Studying the interplay between individual cell behavior and collective cell dynamics in such a tissue context (which often involves heterogeneous cell types) is thus key to understand the mechanical constraints involved in homeostasis as well as cancer growth and invasion, and seek strategies to prevent or intervene on cancer. Mathematical modeling arises as a powerful tool to explore cell fate control, cell proliferation and cell migration patterns and their relationship with cell-cell communication and cell interactions with their niche or in response to external stimuli. In this mini-symposium, we will bring together researchers working in the field of modelling and simulation of tissue mechanics and cell fate in regeneration and cancer. The contributed talks will include population dynamics models as well as off-lattice and lattice-based agent-based models studying cell renewal, cell migration, clonal structure, growth and/or invasion in adult tissue, with emphasis on novel approaches and concepts arising from fits to distinct types of experimental data.

MATHEMATICAL MODELING OF TISSUE MORPHOGENESIS AND REGENERATION

Diane Peurichard (INRIA Paris, Sorbonne Université, LJLL)
Other authors: Pierre Degond, Anastasia Pacary, Jenny Paupert, Marielle Ousset, Anne Lorsignol, Louis Casteilla

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In this talk, we investigate the mechanisms by which organs acquire their functional structure, realize its maintenance over time and rebuild their architecture after injury. We do this by means of two-dimensional Individual Based Models (IBM) of interacting cells and extracellular-matrix fiber elements. The mechanical model first shows that the emergence of organized structures could be explained by simple mechanical interactions between the cells and the collagen fibers. Our assumption is that the fiber network resists the pressure induced by the growing cells and forces them to regroup into clusters. Reciprocally, cell clusters force the fibers to merge into a well-organized network. When applied to adipose tissues, the model produces structures that compare quantitatively well to the experimental observations and seems to indicate that cell clusters could spontaneously emerge as a result of simple mechanical interactions between cells and fibers and surprisingly, vasculature is not directly needed for these structures

to emerge. In the second part of the talk, we extend this model to account for mechanisms of tissue repair after injury, and use it to explore the mechanisms responsible for adipose tissue regeneration. The model successfully generates regeneration or scar formation as functions of few key parameters, and seems to indicate that the fate of injury outcome could be mainly due to extra-cellular (ECM) matrix rigidity. Altogether, these studies point to the essential role of mechanics in tissue structuring and regeneration, and bring a comprehensive view on the role of ECM crosslinking on tissue architecture emergence and reconstruction.

[1] Peurichard, D. et al. (2019). Extra-cellular matrix rigidity may dictate the fate of injury outcome. Journal of Theoretical Biology, 469, 127-136.
https://doi.org/10.1016/j.jtbi.2019.02.017
[2] Peurichard, D. et al. (2017). Simple mechanical cues could explain adipose tissue morphology. Journal of Theoretical Biology, 429, 61-81. https://doi.org/10.1016/j.jtbi.2017.06.030

MODELLING THE INFLUENCE OF LOSS OF E-CATHERIN AND STROMA ATTACHMENT IN CANCER CELL INVASION: MATHEMATIC APPROACH

Pilar Guerrero (Grupo Interdisciplinar de Sistemas Complejos, Departamento de Matemáticas, Universidad Carlos III de Madrid, Madrid, Spain.)
Other authors: S. Melo, P. Guerrero, M. Moreira Soares, J. R. Bordin, F. Carneiro, P. Carneiro, M. B. Dias, J. Carvalho, J. Figueiredo, R. Seruca and R. D. M. Travasso

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Hereditary diffuse gastric cancer (HDGC) evolution depends on E-cadherin dysfunction [1, 2]. We demonstrate experimentally that the low E-cadherin expression strongly correlates with basal epithelial extrusion. Using three different mathematical models, we explore computationally how differential adhesion of the mutated cell to the ECM fibres and epithelial tissue geometry regulates basal extrusion. We introduce a novel phase-field model to describe epithelial tissue dynamics and its interaction with the ECM, and use this model in tandem with a vertex model and a dissipative particle dynamics simulation of epithelial tissues. In these simulations, we observe that the adhesion to the matrix strongly accelerates basal extrusion, thus expecting that, in the progression of HDGC, an increase in cell-ECM adhesion will play an important role. We further observe that the curvature of the epithelial tissue, which increases the mutated cell exposure to the ECM and the mechanical stress imposed on the cell, facilitates the initial steps of cell extravasation. The implementation of different mathematical modelling strategies that yield comparable results strengthens the confidence in these predictions, thus suggesting novel avenues to explore experimentally [3].

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[2] Angst, B. D., Marcozzi, C., Magee, A. I. (2021). The cadherin superfamily: diversity in form and function. Journal of Cell Science, 114(4), 629-641.

https://doi.org/10.1242/jcs.114.4.629
[3] Melo, S. et al. (2023). The ECM and tissue architecture are major determinants of early invasion mediated by E-cadherin dysfunction. Communications Biology, 6(1).
https://doi.org/10.1038/s42003-023-05482-x

NUMERICAL ASSESSMENT OF A MORPHOELASTIC MODEL FOR POST-BURN CONTRACTURES AND HYPERTROPHIC SCARS

Fred Vermolen & Ginger Egberts (Department of Mathematics and Statistics, University of Hasselt, Belgium & Dutch Burns Centre, Beverwijk, The Netherlands)

Common traits of serious burn injuries are hypertrophic scars and skin contractures. In order to alleviate these pathologies, deep understanding of the biological mechanisms is crucially important. This understanding is quantified by the use of mathematical relations so that a link can be made to clinical observation, as well as optimization of therapy is facilitated. In this presentation, we show three-dimensional results, as well as stability analysis in higher dimensions. If time permits, some preliminary results where the computation in the mechanical part of the model is accelerated by the use of machine learning.

EMERGENCE AND CONSEQUENCES OF TRANSCRIPTION FACTOR DYNAMICS DURING DEVELOPMENT

Jochen Kursawe (School of Mathematics and Statistics, University of St Andrews)
Other authors: Joshua Burton, Cerys Manning, Ximena Soto, Magnus Rattray, Nancy Papalopulu

The dynamics of transcription factor concentrations influence cell state in many contexts. For example, oscillations of bHLH transcription factors have been shown to maintain the progenitor state during neurogenesis in multiple organisms. However, the mechanisms regulating such dynamics, as well as the mechanistic link between transcription factor dynamics and cell fate are often unclear. Here, we present theoretical tools that can help illuminate transcription factor dynamics. By comparing mathematical models to transcription factor time series data from single-cell live-imaging microscopy data in zebrafish and mouse models, we identify differences between cell populations by quantifying kinetic rates of transcription, translation, and degradation without further experiments. We further model how differences in transcription factor dynamics can lead to differential gene expression of down-stream targets, and thus changes in cell fate. We use our methods to explain observations in zebrafish hindbrain morphogenesis and mouse spinal cord development.

[1] Burton, J. et al. (2021). Inferring kinetic parameters of oscillatory gene regulation from single cell time-series data. Journal of The Royal Society Interface, 18(182).
https://doi.org/10.1098/rsif.2021.0393
[2] Soto, X. et al. (2020). Dynamic properties of noise and Her6 levels are optimized by miR-9, allowing the decoding of the Her6 oscillator. The EMBO Journal, 39(12).
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MODELLING A PROLIFERATIVE DISORDER OF THE BONE: FIBROUS DYSPLASIA.

Magdalena Caballero (University of Córdoba)
Other authors: Mariia Soloviova, Juan Carlos Beltran Vargas, Luis Fernández de Castro, Juan Belmonte-Beitia, Víctor M. Pérez-García

Fibrous dysplasia (FD) is a disorder of the skeleton in which normal bone is replaced by structurally unsound fibro-osseous tissue, leading to discrete skeletal lesions prone to fracture, deformity, and pain. There is no cure for FD, and there are no known effective medical therapies or treatments. The progression rate of FD lesions and the biochemical factors driving their formation haven't been firmly established. This lack of clarity complicates efforts to explore and apply preventive therapies. Not only is the pathophysiology of FD not fully comprehended, but also there exist undisclosed facets of bone remodeling physiology.

We present a simple mathematical model of FD incorporating the basic known biology of the disease, to gain insight on the dynamics of the involved cell-bone populations, and shed light on its pathophysiology. We develop an analytical study of the model and examine its basic properties, and different numerical simulations provide findings in agreement with the analytical results. We discuss the model dynamics match with known facts on the disease, and how some open questions could be addressed using the model.

[1] Soloviova, M. et al. (2024). A mathematical model for fibrous dysplasia: The role of the flow of mutant cells. arXiv. https://doi.org/10.48550/arXiv.2402.07724

EFFICIENT CELL-BASED MODELLING IN JULIA WITH APPLICATIONS TO DEVELOPMENT AND CANCER.

Gabriel Torregrosa Cortés (Stembryo lab, Universitat Pompeu Fabra.)
Other authors: David Oriola, Universitat Politècnica de Catalunya. Vikas Trivedi, European Molecular Biology Organization, Barcelona Jordi García Ojalvo, Universitat Pompeu Fabra

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Many biological processes as development and cancer require molecular processes in individual cells and collective mechanisms that lead to spatial patterns of the processes being researched. Simulation approaches can give insight in these process, offering a powerful technique to dig into potential treatments and fundamental understanding of the key factors of these problems. Among these methods, cell-based models are a flexible tool for such complex simulations combing cell decisions and spatial organizations. These have been applied successfully to multiple problems in diverse fields of biological research. The main drawback of these models is the complexity to code them and being able to scale their simulations to large systems of cells. In this talk I will introduce the concepts of cell-based modelling and a software developed for their easy implementation in Julia, CellBasedModels.jl. Finally, I will show its application to some biological problems of development and cancer.

[1] Pleyer, J., Fleck, C. (2023). Agent-based models in cellular systems. Frontiers in Physics, 10. https://doi.org/10.3389/fphy.2022.968409
[2] Stichel, D. et al. (2017). An individual-based model for collective cancer cell migration explains speed dynamics and phenotype variability in response to growth factors. npj Systems Biology and Applications, 3(1). https://doi.org/10.1038/s41540-017-0006-3
[3] https://github.com/dsb-lab/CellBasedModels.jl

HYBRID CELLULAR POTTS MODELING OF ANGIOGENESIS: CELL-EXTRACELLULAR MATRIX INTERACTIONS AND CELL-FATE DECISIONS

Roeland Merks (Faculty of Science, Leiden University)

To form new sprouts during angiogenic blood vessel sprouting, cells must coordinate their behavior through biophysical and biochemical cues. My group analyzes single endothelial cell behavior and cell-fate decisions as well as multicellular blood vessel development using a combination of mathematical and experimental approaches. Our central tools are hybrid cellular Potts models (hCPM), in which the lattice-based CPM is coupled with models of the cellular microenvironment and relevant intracellular dynamics. I will start by presenting our recent work on Delta-Notch signaling [1]. Based upon biochemical evidence we extend existing, ordinary-differential equation models of Delta-Notch signaling with cis-inhibition of Notch activity mediated by dimerization of Delta-ligands. The updated model more parsimoniously reproduces published data, showing a non-monotonic response of Notch activity to extracellular Dll4, and also matches previous experimental predictions. I will next present our recent detailed hybrid CPMs of the mechanical and chemical interactions between cells and the extracellular matrix and show how these can be used to study the coordinated cell migration that is seen in angiogenesis. I will discuss our recent hybrid CPM of cellular force transduction in fibrous ECMs [2] and our hybrid CPMs for anisotropic force generation [3]. I will then show recent extensions of this work that incorporates the role focal adhesions, and show first results on strain-dependent digestion of ECMs. Time permitting, I will discuss strategies for experimental falsification and iterative correction of multicellular models of angiogenesis using cell cultures and zebrafish models. Also we invest in computational improvements to advance towards more detailed multicellular models. Altogether, I will present the use of cell-based modeling in analyzing how local cell-microenvironment interactions coordinate cell behavior during angiogenesis.

[1] Chen, Daipeng et al. (2023). A new model of Notch signalling: Control of Notch receptor cis-inhibition via Notch ligand dimers. PLOS Computational Biology, 19(1), e1010169. https://doi.org/10.1371/journal.pcbi.1010169

A SIMPLE PREDICTIVE CELL-FATE MODEL OF EPITHELIAL CLONE DYNAMICS

Gabriel Piedrafita (Universidad Complutense de Madrid)

Cellular decision taking plays a fundamental role in adult tissue homeostasis. Yet, how do tissues orchestrate cell fate commitment to achieve an adequate balance between cell proliferation and terminal differentiation/cellular loss to guarantee homeostatic self-renewal and escape

overgrowth remains unknown. Integrative studies using quantitative lineage tracing to track in vivo labelled clones in transgenic mice in combination with stochastic clonal dynamics modeling have allowed us to dilucidate important principles on cell dynamics in squamous epithelia, such as the skin epidermis and the esophageal epithelium: such epithelia are maintained by a single population of quickly-renewing progenitor cells where daugther fate commitment is subject to certain level of randomness. The outcome of a given cell division is unpredictable; however, probabilistically, overall sibling cells show a preference to commit to anticorrelated fates (i.e. when one divides, the other preferentially differentiates), suggesting that mechanosensing can be a underlying factor controlling the level of stochastic cell fates. In this presentation I will show how such a simple probabilistic model fits WT clone behavior in the mouse esophagus during lifespan, how it can be translated to dilucidate the differentiation-imbalance phenotype underpinning the growth of certain driver mutant clones, and how this knowledge is exploited to infer overall clonal competition constraints in a scenario of mutagenesis using agent-based implementations. I will finish my talk showing advances on an off-lattice model implementing mechanosensing-driven fates. I will discuss the potential relevance of this model for clonal dynamics fitting under various scenarios and for our more realistic understanding of cell fate control in epithelial tissues.

[1] Piedrafita, G. et al. (2020). A single-progenitor model as the unifying paradigm of epidermal and esophageal epithelial maintenance in mice. Nature Communications, 11(1).
https://doi.org/10.1038/s41467-020-15258-0
[2] Colom, B. et al. (2020). Spatial competition shapes the dynamic mutational landscape of normal esophageal epithelium. Nature Genetics, 52(6), 604-614.
https://doi.org/10.1038/s41588-020-0624-3
[3] Murai, K. et al. (2018). Epidermal Tissue Adapts to Restrain Progenitors Carrying Clonal p53 Mutations. Cell Stem Cell, 23(5), 687-699.e8.
https://doi.org/10.1016/j.stem.2018.08.017

NONLINEAR DYNAMICS AND INSTABILITIES IN THE HEART

Blas Echebarria, Roberto Barrio

In this mini-symposium, various aspects of the nonlinear dynamics of the heart will be analyzed and discussed. Special attention will be given to different instabilities that may result in anomalous heart rhythms, some of them life-threatening, such as ventricular or atrial fibrillation. Some well-known examples of cardiac instabilities are early afterdepolarizations (EADs) or alternans, where the action potential presents an abnormal depolarization during the repolarizing phase, in the former, or beat-to-beat alternations in its form or duration, in the latter. Instabilities may also occur in the propagation of the electrical pulse among cardiac cells, or in the dynamics of intracellular calcium, which is the secondary messenger responsible for triggering contraction. We therefore expect that this mini-symposium will provide an overview of the underlying dynamical behaviors in the heart that give rise to life-threatening arrhythmias and whose understanding may, ultimately, help in their prevention or treatment.

BISTABILITY IN THE CONDUCTANCE OF CARDIAC GAP JUNCTIONS

Jean Bragard (Departamento de Física y Matemática Aplicada, Universidad de Navarra)
Other authors: Blas Echebarria

We study the propagation of the cardiac action potential in a one-dimensional fiber, where cells are electrically coupled through gap junctions (GJs). We consider gap junctional gate dynamics that depend on the intercellular potential. We find that different GJs in the tissue can end up in two different states: a low conducting state and a high conducting state. We first present evidence of the dynamical multistability that occurs by setting specific parameters of the GJ dynamics. Subsequently, we explain how the multistability is a direct consequence of the GJ stability problem by reducing the dynamical system's dimensions. The conductance dispersion usually occurs on a large time scale, i.e., thousands of heartbeats. That is highly relevant in studying diseases that develop on a large time scale compared to the basic heartbeat. As in the brain, plasticity, and tissue remodeling are crucial parameters in determining the action potential wave propagation's stability.

[1] Bragard, J. et al. (2021). Conductance heterogeneities induced by multistability in the dynamics of coupled cardiac gap junctions. Chaos: An Interdisciplinary Journal of Nonlinear Science, 31(7). https://doi.org/10.1063/5.0053651
[2] Hawks, C. et al. (2019). Gap Junction Dynamics Induces Localized Conductance Bistability

in Cardiac Tissue. International Journal of Bifurcation and Chaos, 29(08), 1930021. https://doi.org/10.1142/S0218127419300210

UNDERSTANDING THE MATHEMATICAL BIRTH OF EARLY AFTERDEPOLARIZATIONS IN SINGLE CARDIOMYOCYTE MODELS

Roberto Barrio (IUMA, CoDy and Department of Applied Mathematics, Universidad de Zaragoza)
Other authors: J.A. Jover-Galtier, M.A. Martínez, L. Pérez, S. Serrano

Early Afterdepolarizations (EADs) are abnormal behaviors that can lead to cardiac failure and even cardiac death. In this presentation, we investigate mathematically the occurrence and development of these phenomena in a reduced Luo–Rudy cardiac model, and we connect with results given for the Sato et al. biophysically detailed model of a rabbit ventricular myocyte of dimension 27. By examining the bifurcation structure of the model, we elucidate the dynamical elements associated with these patterns and their transitions. Using a fast–slow analysis, we explore the emergence and evolution of EADs in the model.

[1] Sato, Daisuke et al. (2009). Synchronization of chaotic early afterdepolarizations in the genesis of cardiac arrhythmias. Proceedings of the National Academy of Sciences, 106(9), 2983-2988. https://doi.org/10.1073/pnas.0809148106
[2] Barrio, R. et al. (2022). Dynamical mechanism for generation of arrhythmogenic early afterdepolarizations in cardiac myocytes: Insights from in silico electrophysiological models. Physical Review E, 106(2). https://doi.org/10.1103/PhysRevE.106.024402
[3] Barrio, R. et al. (2023). Mathematical birth of Early Afterdepolarizations in a cardiomyocyte model. Mathematical Biosciences, 366, 109088.
https://doi.org/10.1016/j.mbs.2023.109088

THE ROLE OF CALMODULIN REGULATION OF THE RYR2 IN THE ONSET OF CARDIAC ALTERNANS

Enrique Alvarez-Lacalle (Departament de Física, Universitat Politècnica de Catalunya)
Other authors: B. Echebarria, L. Hove-Madsen, S.R.W. Chen

In this presentation, I will show our recent analysis of cardiac alternation in the heartbeat: a characteristic negative marker in the evolution of arrhythmias. Contraction is controlled by intracellular calcium dynamics. This ion increases its concentration strongly once the electrical signal that activates the tissues arrives. The rise in intracellular calcium causes the fibers to

contract. An alternation in the level of calcium rise in each beat is a very important dysfunction to understand that can lead to ventricular fibrillation. Unfortunately, until recently, no conclusive evidence had been found as to the reason behind this alternation. The focus had been correctly placed on the ryanodine receptor, a receptor found on the surface of the sarcoplasmic reticulum, where a large amount of calcium is stored. The opening of this receptor is what causes the calcium inside the reticle to be released into the cytosol. Its control or inactivation has been shown to have a clear role. However, what inactivates RyR2 and how RyR2 inactivation leads to Ca2+ alternans were unknown. In this presentation, I will show how the heartbeat of genetically modified mice, that present dysfunction and changes in calmodulin (CaM), present calcium alternans. We have analyzed these alternans to determine the role of CaM on Ca2+ alternans in intact working mouse hearts. The lab used an in vivo local gene delivery approach to alter CaM function by directly injecting adenoviruses. This data was properly modeled in our research group in Barcelona using a novel numerical myocyte model of Ca2+ alternans that incorporates Ca2+-CaM-dependent regulation of RyR2 and the L-type Ca2+ channel. Data and models showed inactivation of RyR2 by Ca2+-CaM is a major determinant of Ca2+alternans, making Ca2+-CaM dependent regulation of RyR2 an important therapeutic target for cardiac alternans.

[1] Wei, J. et al. (2020). Ca2+-CaM Dependent Inactivation of RyR2 Underlies Ca2+ Alternans in Intact Heart. Circulation Research, 128(4).
https://doi.org/10.1161/CIRCRESAHA.120.318429

OSCILLATIONS IN A MINIMAL CALCIUM MODEL IN CARDIAC CELLS

Blas Echebarria (Departament de Física, Universitat Politècnica de Catalunya)
Other authors: Dylan Valencia, Yohannes Shiferaw, Enrique Alvarez-Lacalle

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Calcium oscillations and waves induce depolarizations in cardiac cells which are believed to cause life-threathening arrhythimas. In cardiac cells, most calcium ions are stored in a membrane-bound structure, the sarcoplasmic reticulum (SR). Release of calcium from the SR to the cytosol is regulated by the ryanodine receptors (RyR), that are themselves sensitive to calcium, resulting in a positive feedback known as calcium induced calcium release (CICR). In this work, we study the conditions for the appearance of calcium oscillations in a model of calcium dynamics that takes into account just the minimal ingredients of the calcium toolkit. This model presents several scenarios depending on the calcium load: two stationary states, one with closed ryanodine receptors (RyR) and most calcium in the cell stored in the sarcoplasmic reticulum (SR), and another, with open RyRs and a depleted SR. In between, calcium oscillations may appear. The minimal model allows us to relate the stability of the oscillating state to the nullcline structure of the system, and find that its range of existence is bounded by a homoclinic and a Hopf bifurcation, resulting in a sudden transition to the oscillatory regime as the cell calcium load is increased. Adding a small amount of noise to the RyR behavior increases the parameter region where oscillations appear and provides a gradual transition from

the resting state to the oscillatory regime, as observed experimentally. Finally, we have also studied the effect of these oscillations on the appearance of oscillations in fibers (1D) and tissues (2D), both when the dynamics is deterministic and when we consider stochastic opening and closing of the RyR.

[1] Marchena, M. et al. (2020). Buffering and total calcium levels determine the presence of oscillatory regimes in cardiac cells. PLOS Computational Biology, 16(9), e1007728. https://doi.org/10.1371/journal.pcbi.1007728
[2] Marchena, M., Echebarria, B. (2018). Computational Model of Calcium Signaling in Cardiac Atrial Cells at the Submicron Scale. Frontiers in Physiology, 9. https://doi.org/10.3389/fphys.2018.01760
[3] Colman, M. A. et al. (2022). Multi-Scale Computational Modeling of Spatial Calcium Handling From Nanodomain to Whole-Heart: Overview and Perspectives. Frontiers in Physiology, 13. https://doi.org/10.3389/fphys.2022.836622

MULTISCALE MATHEMATICAL MODELS IN PHYSIOLOGICAL PROCESSES AND CANCER: FROM SUB-CELLULAR MECHANISMS TO PHENOTYPE SWITCHING AND METASTASIS

Niklas Kolbe, Zuzanna Szymańska

This minisymposium gathers speakers from 7 countries to discuss the interplay between physiological processes and cancer development through the lens of multiscale mathematical modeling.

We present an integrated suite of models, ranging from the intricacies of sub-cellular mechanisms to the emergent behaviors of phenotype switching and metastasis. We begin with the examination of cell migration, transitioning from single-cell motility to collective movements using geometric-bulk-surface partial differential equations. We furthermore investigate the dynamics of breast cancer heterogeneity through the prism of epithelial-mesenchymal heterogeneity, revealing how cell-state transitions and interactions among subpopulations contribute to the cancer's evolutionary trajectory. This meshes with agent-based models that pinpoint the drivers of epithelial-mesenchymal transition (EMT) processes. The cell-signaling of cytokines involved in EMT will be a further topic we address using stochastic models. Focusing on the clinical aspect, our investigation into ovarian cancer progression scrutinizes the EMT's pivotal function in metastasis, aiming to decode the molecular dialogues that empower the cancer cells' invasive prowess. Moreover, we introduce a pathway towards a hybrid, multi-layer metastasis model. Such sophisticated approaches pave the way for simulating cancer's systemic impact, fostering the development of virtual patient avatars for personalized therapeutic interventions. Beyond the cellular interplay, this minisymposium expands the robustness of biological transportation networks by integrating discrete and continuum modeling approaches, exploring their optimality and resilience.

As evidence of the power of mathematical modeling in elucidating the complexities of cancer biology, this minisymposium brings together the multifaceted nature of cancer providing a holistic view that complements our current understanding.

THE INFLUENCE OF THE GEOMETRY AND DOMAIN SIZE FOR A REACTION-DIFFUSION SYSTEM WITH CROSS-DIFFUSION

Gulsemay Yigit (Bahcesehir University)
Other authors: W. Sarfaraz, R. Barreira, A. Madzvamuse.

In this talk, we present a domain-dependent analysis of reaction-diffusion systems to understand the role of geometry and linear cross-diffusion in pattern formation. By deriving conditions on the domain length for rectangular, circular and annular geometries, we generate parameter spaces associated with Turing difusion-driven instability, Hopf and trascritical instabilities. We explore whether selection of a sufficiently large domain size, together with the appropriate selection of parameters, can give rise to the spatial and spatiotemporal patterns on convex and non-convex geometries. To support theoretical findings, finite element numerical simulations on rectangular, circular and annular geometries are presented.

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COMPUTATIONAL INVESTIGATION OF HETEROGENEOUS CELL PHENOTYPES IN THE TUMOUR MICROENVIRONMENT

Raluca Eftimie (Université de Franche-Comté, France)

Tumour microenvironment is characterised by heterogeneity at various scales: from various cell populations (immune cells, cancerous cells...) and various molecules that populate the microenvironment; to phenotype heterogeneity inside the same cell population (e.g., cancer cells with different phenotypes; immune cells with different phenotypes and different functions). There is also temporal heterogeneity in cells' phenotypes as cancer evolves through time, and spatial heterogeneity inside the tumour microenvironment. Here we focus on modelling and investigating computationally the temporal evolution of cell phenotypes inside the tumour microenvironment. To this end we focus not only on cancer cells, but also on macrophages (immune cells that can be found in high numbers in some solid cancers). The results suggest that changes in the clonal evolution of tumours are associated with changes in the phenotype evolution of macrophages (from the anti-tumour M1 phenotype to the pro-tumour M2 phenotype). The results have potential implications on the various therapies aimed at reversing cellular phenotypes in an attempt to improve cancer outcomes.

CELL-STATE TRANSITIONS AND FREQUENCY-DEPENDENT INTERACTIONS AMONG SUBPOPULATIONS TOGETHER EXPLAIN THE DYNAMICS OF SPONTANEOUS EPITHELIAL-MESENCHYMAL HETEROGENEITY IN BREAST CANCER

Paras Jain (Indian Institute of Science, India)

Individual cells in a tumour can be distributed among Epithelial (E) and Mesenchymal (M) cell states, as characterised by the levels of canonical E and M markers. Even after E and M (E-M) subpopulations are isolated and then cultured independently, E-M heterogeneity can re-equilibrate in each population over time, sometimes regaining the initial distribution of the parental cell population. However, it remains unclear which population-level processes give rise to the dynamical changes in E-M heterogeneity observed experimentally, including 1) differential growth, 2) cell-state switching, and 3) frequency-dependent growth or state-transition rates. Here, we analyse the necessity of these three processes in explaining the dynamics of E-M population distributions as observed in PMC42-LA and HCC38 breast cancer cells. We find that growth differences among E and M subpopulations, with and without any frequency-dependent interactions (cooperation or suppression) among E-M sub-populations, are insufficient to explain the observed population dynamics. This insufficiency is ameliorated by including cell-state transitions, albeit at slow rates, in explaining both PMC42-LA and HCC38 cells data. Further, our models predict that treatment of HCC38 cells with TGFβ signalling and JAK2/3 inhibitors could significantly enhance the transition rates from M state to E state, but does not prevent transitions from E to M. Finally, we devise a selection criterion to identify the next most informative time points for which future experimental data can optimally improve the identifiability of our estimated best fit model parameters. Overall, our study identifies the necessary population-level processes shaping the dynamics of E-M heterogeneity in breast cancer cells.

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MODELING HETEROGENEOUS GENE EXPRESSION RESPONSES TO TGFβ STIMULATION

Karen Amaral Oliveira (University of Stuttgart, Germany)

Transforming Growth Factor-beta (TGFβ) is a highly versatile cytokine that plays an important role in a wide range of cellular processes, such as cell growth, differentiation, and immune responses. The signaling of TGFβ is facilitated by the SMAD family of proteins which function as transcription factors, transmitting from the cell surface to the nucleus to ultimately induce large-scale gene expression changes. When we analyze a population of cells individually, numerous cell-specific patterns emerge even when the initial conditions are seemingly the same. It is essential to consider such heterogeneity to fully understand gene expression responses and cell fate decisions induced by TGFβ in population of cells. By introducing mathematical models of intracellular signaling and gene regulation, we quantitatively describe the relationship between TGFβ stimulation and cellular heterogeneity from single-cell data. We consider both stochastic and deterministic noise in our models, and reveal patterns of heterogeneous decision

making that contribute to understanding TGFβ signaling and its involvement in cellular processes and disease progression.

AGENT-BASED MODELLING OF HETEROGENEOUS EMT SCENARIOS HIGHLIGHTS NUCLEAR POSITIONING AND PROTRUSIONS AS MAIN DRIVERS OF EXTRUSION

Steffen Plunder (Kyoto University, Japan)
Other authors: M.A. Ferreira, C. Danesin, B. Glise, S.M. Aceituno, E. Theveneau

Epithelial-Mesenchymal transition (EMT) is a key process during development, fibrosis and cancer. The typical presentation of EMT includes a progression of events after which cells detach from their surrounding cells, reorient themselves to leave the epithelium basally and then establish their migratory function which can result in invasion. However, it is now accepted that there are multiple EMT scenarios and that cells possibly follow ineffective progressions of EMT events. It is in particular unclear which of the EMT events ensures basal extrusion and in the cancer setting it would be desirable to find ways to prevent basal extrusion to stop metastasis at its beginning. To assess the key EMT events leading to extrusion and the role of heterogeneity, we developed an agent-based model for pseudostratified epithelium. Since the epithelium contains some congested areas, we used a simple but effective numerical method called position-based dynamics to overcome numerical stiffness issues and speed-up the model to enable large ensemble simulations. The ensemble simulations gave insight into the role of heterogeneity and the robustness of this pathway. Our simulated and biological data point to a key role of nuclear positioning and early onset of migratory activity to generate timely basal extrusion of cells and suggest a non-linear model of EMT allowing multiple scenarios to co-exist.

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EXPLORING THE ROLE OF EMT IN OVARIAN CANCER PROGRESSION AND METASTASIS

Sam Oliver (Swansea University, United Kingdom)

The progression of cancer tumours is highly dependant on the crucial role played by Epithelial-to-Mesenchymal Transition (EMT), rendering treatments less effective for patients. EMT involves a cellular phenotype shift, leading to altered behaviours such as heightened drug resistance, increased cell plasticity, and enhanced cell motility. This cell movement amplifies the

metastatic potential of tumours, with metastatic cancers responsible for 90% of all cancer-related deaths. Quantifying and understanding this transition has become imperative. In this study, a multiscale mathematical framework is employed to investigate EMT and its temporal impact on two distinct cell lines, OVCAR-3 and SKOV-3. The model, based on a Physicell framework, is a 3D agent-based multiscale model incorporating experimentally observed cellular changes and microenvironment effects. Due to the diverse tumour layouts of OVCAR-3 and SKOV-3, the model is highly adaptable, facilitating rapid and comprehensive in silico analysis without substantial modifications to core dynamics. The model accurately captures biological observations and trends in tumour growth, establishing its viability for making predictions and gaining insights. The study identifies key processes in the multistage EMT, utilising sensitivity analysis to highlight input parameters with the most significant impact on the tumour over time.

A DATA-DRIVEN STOCHASTIC MODEL OF TGFB SIGNALING IN SINGLE CELLS

Niklas Kolbe (RWTH Aachen University, Germany)
Other authors: A. Diez, S. Lee

The cytokine TGFb plays an important role in cancer progression as it is involved in both preventing uncontrolled tissue growth and triggering epithelial-to-mesenchymal transition. Time-resolved single-cell measurements show that its signaling exhibits temporal stochastic bursts which are dose-dependent and whose number and magnitude correlate with cell migration. For quantitative insights into mechanisms underlying fluctuations at various time scales we propose a new stochastic modeling approach for single-cell TGF-β/SMAD signaling that we present in this talk. Our approach is based on burst analysis and stochastic differential equations and explains with high computational efficiency heterogeneous signaling dynamics between the cells found in the experimental data.

DISCRETE AND CONTINUUM MODELING OF ROBUST BIOLOGICAL TRANSPORTATION NETWORKS

Jan Haskovec (King Abdullah University of Science and Technology, Saudi Arabia)

Motivated by recent results on formation and adaptation of biological transport networks, we study a discrete model consisting of an energy consumption function constrained by a linear system on a graph. We discuss how structural properties of the optimal network patterns, like sparsity and (non)existence of loops, depend on the convexity/concavity of the metabolic part of the energy functional. We then introduce robustness of the network in terms of algebraic connectivity of the graph and explain its impact on the network structure. Passing to the

continuum limit as the number of edges and nodes of the graph tends to infinity, we recover a nonlinear system of PDEs. This elliptic-parabolic system consists of a Darcy's type equation for the pressure field and a reaction-diffusion equation for the network conductance. We explain how the robustness property is reflected on the level of the PDE description. We give both analytical results and systematic numerical simulations for the PDE system, providing interesting insights into the mechanisms of network formation and adaption in biological context.

EMERGING DATA DRIVEN APPROACHES FOR INCREASING THE PREDICTION AND UNDERSTANDING OF BIOLOGICAL PROCESSES.

Joanne Dunster, Sara Jabbari

The emergence of extensive data in the field of biology presents a variety of new challenges and possibilities. Our mini-symposium is designed to focus on methodologies that leverage these expansive datasets to identify and quantify underlying biological patterns, integrating this information into practical models of use to biologists. The event will delve into various mathematical and statistical techniques such as identifiability, feature selection, the use of biological data to better inform model selection and the integration of omics data while covering a wide range of applications including ion channels, atherosclerosis, Alzheimer's, washing detergents, cell migration and PTSD. Given the importance of integrating data into mathematical models to optimise their reliability we anticipate this session being of interest to the broad mathematical biology community.

We have included talks from researchers from different disciplines ranging from mathematics, statistics and computing, believing that the synthesis of these methods is important to better integrate larger datasets. The speakers include 2 Phd students, and 2 established researchers with a mix of genders and backgrounds.

FEATURE SELECTION AND PARAMETER INFERENCE WITH SPARSLEY SAMPLED DATA VIA LASSO AND GLOBAL OPTIMIZATION

Rahma Abdulahi (University of Birmingham)
Other authors: S. Jabbari, D. J. Smith, C. Amador

Motivated by the challenge of fitting a nonlinear system involving a high number of possible parameters to infrequently sampled data, we apply a LASSO penalty function in conjunction with global optimization. The LASSO penalty allows for the gradual removal of parameters in a model, allowing for a reduction in the number of irrelevant features and the dimensions of the parameter search space. In this talk, we will cover the application of the method on a nonlinear semi-mechanistic model of stain removal developed by Procter & Gamble to aid in the formulation of detergents.

Through multicore computing, we obtain consistent global optima across a range of LASSO penalty hyperparameters. The key features in determining detergent performance are then identified through the L-curve criterion and cross validation. We discuss the potential application of the approach in biochemical systems with large numbers of parameters and infrequently

sampled time series data.

BUILDING INTERPRETABLE MACHINE LEARNING MODELS FROM OMICS DATA TO BETTER UNDERSTAND BIOLOGY.

Rachel Cavill (Maastricht University)

Many machine learning techniques when combined with complex omics datasets can produce black-box models, which may be able to predict well, but are difficult or even impossible to use for generating biological understanding. This talk will explore how the interplay between the methods chosen and new approaches to generating explainable and interpretable models can help us get much more from our datasets. In particular we will focus on a set of (mostly) linear models called "multi-variate models" which are particularly well-suited to dealing with the collinearity present in omics data, and explore how background knowledge surrounding pathways and other functional sets of entities can be used to enhance the interpretability of these models. It will also address how these methods can be extended for use in data integration when multiple omics datasets are collected on the same samples or people in parallel.

MECHANICAL REGULATION AND CELL CYCLE DYNAMICS IN MODELS OF COLLECTIVE CELL MIGRATION

Carles Falcó (University of Oxford)
Other authors: J. A. Carrillo, D. J. Cohen, R. E. Baker

Cells have the ability to adapt their division rates in response to mechanical checkpoints, yet we do not fully understand how cell proliferation regulation impacts cell migration phenomena. In this talk, we present a minimal continuum model of cell migration with cell cycle dynamics which accounts for the mechanical regulation of cell proliferation. By combining minimal mathematical modelling, Bayesian inference, and recent experimental data, we quantify the impact of mechanical constraints across different cell cycle stages in epithelial tissue expansion experiments. Our model suggests that cells sense local density and adapt cell cycle progression in response, during G1 and the combined S/G2/M phases, providing an explicit relationship between each cell cycle stage duration and local tissue density, which is consistent with several experimental observations. Finally, we compare our mathematical model predictions to different experiments studying cell cycle regulation and present a quantitative analysis on the impact of mechanical constraints on cell migration patterns.

REDUCING UNCERTAINTY IN ION CHANNEL MODELS VIA EXPERIMENTAL DESIGN AND ACCOUNTING FOR EXPERIMENTAL ARTEFACTS

Gary Mirams (University of Nottingham)
Other authors: J. Shuttleworth, F. Patten-Elliott, S. Preston, M. Clerx

The field of electrophysiology continues to use the same approach to voltage-clamp protocol design that Hodgkin & Huxley used in the 1940s, in terms of designs that enable model parameter values to be estimated manually from graph paper. We have been developing short, high-information voltage clamp protocols to characterise ion currents more efficiently. I will discuss various rationales for designs that consider parameter identifiability, model selection and minimising experimental artefacts. We then use computational optimisation to fit simple mathematical models to the resulting currents, and use them to predict the results of conventional voltage clamp protocols. We also use an additional mathematical model to account for patch clamp artefacts to consolidate information from different patch clamp recordings more reliably, as well as a new ensemble-of-experimental-designs approach to get a bound on the effects of model discrepancy from reality.

RECENT DEVELOPMENTS IN BIOFILM MODELLING

Maria Rosaria Mattei, Luigi Frunzo

Biofilms have inspired intensive investigations from researchers due to their complexity, heterogeneity, and ubiquity in both natural and artificial environments. Biofilms are likely involved in most (if not all) aspects of microbiology, and they can be linked to important societal issues such as antimicrobial resistance, microbial corrosion and chronic infectious diseases, but also to the positive aspects related to wastewater treatment, food production and bioremediation. How do biofilms form? How do they thrive? What are they made of? How do they interact with the surrounding environment? All these questions and many others have been at the heart of scientific research for decades. Extensive mathematical modelling has emerged as a widely accepted tool for the understanding of the nonlinear, multidimensional, and multiscale nature of these complex microbial systems. A wide variety of models have been proposed to understand biofilm mechanics and mechanisms, including individual based, cellular automata and immersed boundary approaches, phase-field models, mixture theory models, free boundary problems, and degenerate diffusion equations. This minisymposium addresses different biofilm applications, modelling approaches and methods, and is aimed to foster collaboration and knowledge-sharing among researchers working in this area.

IMMERSED BOUNDARY MODELS FOR BIOFILM SPREAD AND RESPONSE TO ANTIBIOTICS

Ana Carpio (Universidad Complutense de Madrid (Spain))
Other authors: R. González Albaladejo

We propose an immersed boundary approach to simulate the spread of bacterial biofilms on interfaces including bacterial metabolism and the action of antibiotics. We represent bacterial membranes by boundaries immersed in a fluid matrix, subject to interaction forces. We implement dynamic energy budget rules to describe the metabolism of each bacterium (growth, division and death) informed by environmental concentrations of nutrients, toxicants and substances released by the cells. The interaction between cells, and their interaction with the environment is represented by appropriate forces. Numerical simulations illustrate the behavior of small aggregates of spherical and rod-like bacteria. The immersed boundary approach allows us to investigate geometrical arrangements as bacteria divide and die, competition of different shapes and the formation of porous structures. The dynamic energy budget framework allows us to incorcoporate antibiotic effects on the biofilm and resistance mechanisms. We show that cocktails of antibiotics targeting dormant and active bacteria can entirely eradicate

a biofilm.

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ESTIMATING BIOFILM VISCOELASTIC PROPERTIES USING A BAYESIAN FRAMEWORK

Nick Cogan (Department of Mathematics, Florida State University (USA))
Other authors: M. Nooranidoost, P. Stoodley, E.S. Gloag

Biofilms are well known to exhibit viscoelastic response to physical forces. Specific viscoelastic models have been used for at least 30 years to provide a framework to describe the biofilm rheology when a biofilm is exposed to deformations experiments. However, given the more recent understanding of the multicomponent nature of biofilms, including specific EPS constituents such as PEL, PSL and alginate, it is worth revisiting these measurements to understand the role of the constituents in the rheological properties. In this talk, we will describe a Bayesian framework for estimating rheological properties for deletion and over-expression mutant biofilms with both creep recovery and frequency sweep data.

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BIOFILM ACCUMULATION AND MASS TRANSPORT IN POROUS MEDIA MODELED BY A PDE-ODE COUPLED SYSTEM DERIVED FROM A WANNER-GUJER LIKE COMPARTMENT MODEL OF BIOFILM REACTORS

Hermann Eberl (Department of Mathematics and Statistics, University of Guelph (Canada))

In 1995, Wanner and Cunningham proposed to model biofilm accumulation and mass transport in a porous medium by a finite number of biofilm reactors in series [1]. In the single species case, each such reactor is described by an ODE, the evaluation of the right hand side of which requires the solution of a two-point boundary value problem. Taking the number of such reactors to infinity and shrinking them to a point, we obtain a quasi-linear PDE-ODE coupled system on the macroscale. We show that this limit procedure in the case of Monod growth kinetics leads on the macroscale to a biofilm description akin to that in Platte's zero-dimensional biofilm reactor model, reviewed in [2]. This upscaling procedure is sensitive to the choice of mesoscopic detachment model. We show that first order detachment and Rittmann's shear dependent detachment model from 1982 can be incorporated. The second order detachment model and a shear dependent detachment model that we introduced in 2012 cannot be recovered in this procedure. We will also show, by numerical simulation, that neglecting diffusion in main flow direction (as was the case in the original compartmentalised description) in this process underestimates quenching length, i.e. the distance over which the substrate is degraded. Time permitting we will also show how this model framework can be applied to simulate bioreduction of Uranium in soils. This is joint work with Harry Gaebler and Emma Bottomley.

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MULTISCALE MODELING OF MICROBIAL COMMUNITY METABOLISM

Isaac Klapper (Department of Mathematics, Temple University (USA))

Outside of laboratories, microbial communities (biofilms and other types) often exist in relatively stable environments where, on average, resource quality and quantity are predictable. In these conditions, these communities are able to organize into tuned chemical factories, efficiently turning resources into biomass and waste byproducts. To do so, physical, chemical, and biological constraints must be accommodated. Techniques to model this organization will be discussed. In particular, the importance of coupling cell scale metabolic information to community scale transport processes will be emphasized. To illustrate, we couple (microscale) full genome fba metabolic models to biofilm models including macroscale transport.

MODELLING HETEROGENEITY, ADAPTATION AND EVOLUTION IN CANCER

Carine Legrand, Céline Bonnet

Heterogeneity is inherent to biological processes, arising from cell-to-cell variability and intrinsic stochastic fluctuations, whose origin resides in the complexity of the underlying biochemical reaction networks. In cancer, sources of heterogeneity are embodied by inter- and intra-tumoral heterogeneity, by phenotypic plasticity of cells and by evolution, leading to adaptation and resistance. To decipher the dynamics at stake, and finally propose personalized therapy, represents a major challenge. Mathematical modelling is able to provide insights, by quantifying and leveraging experimental data, but of great importance is the ability to distinguish between different sources of heterogeneity that have qualitatively different origins and characteristics. In this minisymposium, we present recent advances which explore heterogeneity across scales, from heterogeneity in gene expression, mutation distribution, to protein expression and evolution. First, we present a model of gene states to investigate the steady-state dynamics of gene expression, as well as whether thermodynamic considerations allow for greater distinguishability in heterogeneity-type. Then, we study a bi-type branching process to investigate the influence of adaptation on mutation distribution. Further, a system of differential equations, informed by in-vitro experiments, allows to characterize the adaptation of a phenotypically heterogeneous population. Finally, a fast-growth model, integrated with external estimates, is employed to characterize evolution in a whole-genome dataset, and to identify subgroups of patients.

THE STATISTICAL PHYSICS OF GENE EXPRESSION AND MRNA EXPRESSION HETEROGENEITY

James Holehouse (The Santa Fe Institute, USA)

How far-from-equilibrium is gene expression? For a quintessential two gene-state model, with mRNA expression in both gene states, we conduct a probability flux analysis of the steady state probability distribution and show that the system expresses marginal detailed balance on the level of the mRNA number. However, the steady state is not an equilibrium due to the nature of gene state transitions, as elucidated by the analytic formula we derive for the entropy production rate starting from the microscopic master equation. This also implies that there are birth-death processes, with time-dependent birth rates, which both satisfy detailed balance and have a non-zero entropy production rate. Notably, the microscopic dynamics can be irreversible, while the coarse-grained marginal dynamics appear to satisfy detailed balance.

Finally, we speculate that the bursty nature of gene expression may be accounted for by the low entropy production rate in such conditions using methods connecting non-elementary Markov models to Crooks' fluctuation theorem, leading to free energy efficient expression.

SITE FREQUENCY SPECTRUM OF A RESCUED POPULATION UNDER RARE RESISTANT MUTATIONS

Céline Bonnet (Inria, ENSL, UMPA, CNRS UMR, France)
Other authors: H. Leman

The aim of this talk is to study the impact of resistance acquisition on the distribution of neutral mutations in a cell population under therapeutic pressure. The cell population is modeled by a bi-type branching process. Initially, the cells all carry type 0, associated with a negative growth rate. Mutations towards type 1 are assumed to be rare and random, and lead to the survival of cells under treatment, i.e. type 1 is associated with a positive growth rate, and thus models the acquisition of a resistance. Cells also carry neutral mutations, acquired at birth and accumulated by inheritance, that do not affect their type. We describe the expectation of the"Site Frequency Spectrum" (SFS), which is an index of neutral mutation distribution in a population, under the asymptotic of rare events of resistance acquisition and of large initial population. Precisely, we give asymptotically-equivalent expressions of the expected number of neutral mutations shared by both a small and a large number of cells. To identify the influence of relatives on the SFS, our work also lead us to study in detail subcritical binary Galton-Watson trees, where each leaf is marked with a small probability. As a by-product of this study, we thus provide the law of the generation of a randomly chosen leaf in such a Galton-Watson tree conditioned on the number of marks.

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DETERMINISTIC MODELLING OF CANCER EVOLUTIONARY DYNAMICS: A PHENOTYPE-STRUCTURED PDE APPROACH

Chiara Villa (LJLL, Sorbonne Université, Paris, France)
Other authors: L. Almeida, M.A.J. Chaplain, J.A. Denis, N. Ferrrand, T. Lorenzi, F. Padovano, A. Prunet, M. Sabbah

Glucose and oxygen are primary energy sources for cancer cells. Several lines of evidence support the idea that changes in gene and protein expression levels (e.g. MCT1, HIF1) elicit metabolic reprogramming of cancer cells in nutrient-poor environments, promoting cancer cell survival and disease progression. Moreover, the coexistence within the same tumour of cancer cells that express different phenotypic characteristics poses a major obstacle to successful anti-cancer therapy and management of disease relapse. A more in-depth theoretical understanding of the evolutionary processes at the root of cancer cell adaptation to nutrient deprivation and the emergence of intratumour phenotypic heterogeneity can be achieved through analysis and numerical simulation of phenotype-structured population models. The focus of this talk is on non-local partial differential equations modelling the adaptive dynamics of a population of cancer cells structured by protein expression levels. First, I will present an experimentally-informed mathematical model of a spatially well-mixed population, which was calibrated with data from in vitro experiments on glucose-deprived aggressive cancer cells, including proteomics data. Then, I will present spatially-explicit extensions of the model and discuss the additional analytical challenges introduced by spatial movement, and how a formal Hamilton-Jacobi approach can be used to obtain weak solutions in appropriate asymptotic limits. The analytical and numerical results presented shed light on the mechanisms underlying protein expression changes observed in glucose-deprived aggressive cancer cells during in vitro experiments, and the evolutionary determinants of intratumour phenotypic heterogeneity in vascularised tumours.

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TIME-RESOLVED, INTEGRATED ANALYSIS OF CLONALLY EVOLVING GENOMES

Carine Legrand (Université Paris Cité , Génomes, biologie cellulaire et thérapeutique U944, INSERM, CNRS, Paris, France)
Other authors: R. Andriantsoa, P. Lichter, G. Raddatz, F. Lyko, M. Duchmann, R. Itzykson, A. Puissant

Genomes evolve under the accumulation of mutations, and under the pressure of selective forces. While additional mechanisms are at play in sexually reproducing species, this is not

the case in clonal genomes, and in particular in cancer, where only a subset of parameters are needed to understand expansion, tumor persistance, and the chronology of the tumor. Here we employed a deterministic model of fast-growing tumors. We observed that selection was non-observable in our model, and remedied it by obtaining this information from a distinct source. Further, we used clock-like mutational signatures as a surrogate for time. Combining the model and these additional estimates, we expressed the expansion parameters of the tumor. We further expressed the fitness ratio at the transition between two sampling timepoints. We applied our model to 42 pairs of primary and relapsed samples of glioblastoma tumors. We obtained a nuanced depiction of selection forces, categorized tumors into four subgroups using expansion parameters, and determined the fitness ratio, which was associated with patient survival. We will introduce a reworking of this framework to the slow-pace progression from a preleukemic syndrom into acute myeloid leukemia.

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DATA-DRIVEN APPROACHES IN INFECTIOUS DISEASE MODELING

Necibe Tuncer, Stanca Ciupe

Mathematical modeling of infectious diseases is essential for understanding the mechanisms involved in disease transmission, predicting the course of infectious diseases, and facilitating effective control measures to prevent their spread. In particular, using well-formulated, parametrized models which are validated with data allows us to respond to outbreaks more effectively. This mini-symposium will focus on the development of sophisticated mathematical models, the application of novel computational techniques, and the validation of models using real-world data. The symposium seeks to facilitate collaboration, idea exchange, and the advancement of data-driven approaches to infectious disease dynamics. Some potential topics to be covered in the mini-symposium will be (i) modeling control strategies for infectious diseases, (ii) multiscale epidemic models, (iii) validation and uncertainty quantification (iv) identifiability analysis.

SIMPLE MODELS OF EPIDEMIC CONTROL THROUGH MASS-TESTING

Andrea Pugliese (University of Trento)
Other authors: M. Sabbatino, S. Sottile

During the course of the COVID-19 pandemic, mass testing followed by isolation of the positive individuals, has been suggested as a potential strategy to control the epidemic, especially in restricted settings (such as schools or workplaces), before vaccines were available. The effectiveness of the strategy, possibly completed with contact tracing, has been examined in several papers [1,2,3], mainly through simulations. Here we examine the conditions under a test-and-isolate strategy could actually control an epidemic for simple models of SIR or SEIR type, under different modalities of administering the testing. It is often possible also to compute the reduction in the value of R0 and consequently in the final attack ratio. The possibility of extending the models to include contact tracing will also be discussed. Although the models are very simple and cannot adequately describe the actual complexities of epidemic dynamics and control strategies, we believe it can be useful to provide a theoretical background against which predictions from structured simulation models can be compared.

UNDERSTANDING SHORT-TERM AND LONG-TERM VIRUS DYNAMICS: LESSONS FROM HEPATITIS B INFECTIONS

Stanca Ciupe (Virginia Tech, USA)

Understanding short and long-term viral dynamics following therapy or immune interventions can help uncover previously unknown feedback interactions and drug's mode of action. In this presentation, I will investigate short and long-term dynamics in hepatitis B viral infection following therapy with ARC-520, an RNA interference drug, in humans. We studied the effect of the drug by developing mathematical models of within-host dynamics and comparing them to patient data. We examined biological hypotheses describing the different outcomes and proposed mechanisms of action explaining post-intervention control. The results can help identify treatment markers of cure.

MULTI-SCALE MODELLING OF INHALATIONAL ANTHRAX

Bevelynn Williams (University of Leeds)

Inhalational anthrax, caused by the bacterium Bacillus anthracis, is a disease with very high fatality rates. Due to the significant risk posed if the bacterium was to be intentionally used as a bioweapon, it is important to be able to defend against such an attack and to make optimal decisions about treatment strategies. Mechanistic mathematical models can help to quantify and improve understanding of the underlying mechanisms of the infection. In this talk, I will present a multi-scale mathematical model for the infection dynamics of inhalational anthrax. This approach involves constructing individual models for the intracellular, within-host, and population-level infection dynamics, to define key quantities characterising infection at each level, which can be used to link dynamics across scales. At the intracellular scale, we consider a stochastic, Markov chain model for the intracellular infection dynamics of B. anthracis in a single phagocyte, incorporating spore germination and maturation, bacterial proliferation and death, and the possible release of bacteria due to cell rupture. This model is parameterised with in vitro experimental data and used to predict the distribution of outcomes from this host-pathogen interaction. For example, it is used to estimate the number of bacteria released upon rupture of an infected phagocyte. This key quantity is then incorporated into a within-host model of infection, which aims to provide an overall understanding of the early progression of the infection. Furthermore, this stochastic modelling approach allows us to quantify and predict individual infection risk and time to symptom onset following exposure.

THE EFFECT OF MODEL STRUCTURE AND DATA AVAILABILITY ON USUTU VIRUS DYNAMICS AT THREE BIOLOGICAL SCALES

Necibe Tuncer (Florida Atlantic University)
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Understanding the epidemiology of emerging pathogens, such as Usutu virus infections, requires systems investigation at each scale involved in the host-virus transmission cycle, from individual bird infections, to bird-to-vector transmissions, and to Usutu virus incidence in bird and vector populations. For new pathogens field data is sparse, and predictions can be aided by the use of laboratory-type inoculation and transmission experiments combined with dynamical mathematical modeling. In this study, we investigated the dynamics of two strains of Usutu virus by constructing mathematical models for the within-host scale, bird-to-vector transmission scale, and vector-borne epidemiological scale. We used individual within-host infectious virus data and percent mosquito infection data to predict USUV incidence in birds and mosquitoes. We addressed the dependence of predictions on model structure, data uncertainty, and experimental design. We found that uncertainty in predictions at one scale change predicted results at another scale. We proposed *in-silico* experiments that showed that sampling every twelve hours ensures practical identifiability of the within-host scale model. At the same time, we showed that practical identifiability of the transmission scale functions can only be improved under unrealistically high sampling regimes. Instead we proposed optimal experimental designs and suggested the types of experiments that can ensure identifiability at the transmission scale and, hence, induce robustness in predictions at the epidemiological scale.

MODELING, REGULATION AND CONTROL OF CELLULAR NETWORKS

Tomas Gedeon, Madalena Chaves

Cellular networks are at the heart of cell responses to external signals. Signaling, metabolic and other regulatory pathways all depend on cellular networks to interpret external stimuli and generate a cell response. Malfunctioning of an organism and disease are often the outcomes of disfunction in a cellular network. For this reason, it is important to study the dynamics in cellular networks and assess strategies for correcting or controlling network disfunction.

Cellular networks usually involve a large number of elements and are challenging to model. Therefore there is a range of mathematical formalisms currently used in the literature notably discrete models such as Boolean networks, switching or piecewise linear ODE systems, but also constraint-based models. Using such formalisms, it is often possible to analyze dynamics and devise control strategies to mitigate, reverse, or correct malfunctioning in cellular networks.

HOW DO BACTERIA ADAPTIVELY CONTROL THEIR GROWTH RATE IN FLUCTUATING ENVIRONMENTS?

Robert Planqué (Vrije Universiteit Amsterdam)
Other authors: F. J. Bruggeman, J. Hulshof

Single celled organisms such as bacteria are able to tune enzyme levels that catalyze the reaction pathways by which they eventually make new copies of themselves. Depending on nutrient conditions, more or less enzyme is invested in different parts of their reaction network, so that reaction rates are constantly high, and cellular growth rate is maximized. In this talk I will present an adaptive control mechanism designed to solve this problem. It involves an ODE system with two sets of algebraic equations attached. Through a detailed analysis of the steady state and maximization problems, we show that the adaptive control is actually globally stable for a wide variety of pathways. This suggests that real bacteria might actually be able to perform such adaptive control mechanisms using hardwired gene regulation.

THE LOGICAL MODELLING APPROACH DEMONSTRATED THROUGH THE ANALYSIS OF A HYBRID EPITHELIAL-MESENCHYMAL NETWORK

Claudine Chaouiya (Aix-Marseille University)

I will briefly introduce a published logical model of the Epithelial-to-mesenchymal transition (EMT) network. With this model, we aimed at assessing the control of cancer-associated phenotypes through selected microenvironmental signals control along the EMT continuum, characterised by different qualitative degrees of cell adhesions by adherens junctions and focal adhesions. I then intend to illustrate the use of formal methods (model-checking, ASP) to get insights in the model properties and to propose relevant control strategies.

CELL GEOMETRY CONSTRAINS ESCHERICHIA COLI GROWTH RATE, RESPIRATION CAPACITY, AND INTERACTIONS WITH ENVIRONMENT

Tomas Gedeon (Montana State University)
Other authors: A. E. Beck, M. Benitez, R. Mahadevan, and R. P. Carlson.

We present a predictive and quantitative theory that defines the intersection of membrane protein capacity, cell geometry, and central metabolism. The theory identifies a biophysical basis for maximum growth rate, overflow metabolism, electron transport chain efficiency defined by the P/O number and provides quantification of maintenance energy fluxes. Our analysis suggests, contrary to common arguments, that E. coli batch cultures maximize neither growth rate nor biomass yield. Instead, E. coli operates at intermediate growth rates and yields while maximizing the areal density of ATP synthase complexes, thereby maximizing rates of substrate energy dissipation. Our analysis does not consider resource investments into the cytosolic proteome, demonstrating the predictive power of a surface area constraint alone.

TOLERANT VS. SENSITIVE: DECIPHERING HETEROGENEOUS CELLULAR RESPONSE VIA MATHEMATICAL MODELING OF SINGLE-CELL DYNAMICS

Giada Fiandaca (Inria Center at Université Côte d'Azur)
Other authors: M. Péré, J. Roux, M. Chaves

Variability in cellular responses to anticancer drugs is an inherent characteristic within clonal cell populations, impairing overall treatment efficacy. This has been exemplified with

the administration of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), where single-cell studies have unveiled distinct responses of cells within the same clonal population. These studies suggest that both drug-sensitive and drug-resistant phenotypes may arise from the same pathway structure, and the observed variability could result from fluctuations in the initial concentrations of proteins [2], although this hypothesis remains incompletely investigated. In previous work, we developed a mathematical model describing the core reactions involved in the extrinsic apoptosis pathway triggered by TRAIL [3]. Here, we will present a detailed analysis of this model, with the goal of extending it to make it a better predictive tool in forecasting the cell response phenotype. By calibrating the model to experimental single-cell trajectories from a clonal population of cells, we can indeed characterize the differential dynamics between tolerant and sensitive phenotypes in terms of parameter distributions. This allows us to discern a primary set of reactions leading to heterogeneous responses, with an emphasis on identifying new regulatory reactions that are key factors in leading to a phenotype divergence. In particular, our preliminary results identify a significant difference in the deactivation mechanism of the cysteine protease caspase-8 (C8), which is an initiator of extrinsic apoptosis, as well as a difference in the activation mechanism of C8, in a trend suggesting a dose dependency. Finally, the identified differences can impact cancer therapeutic development by revealing the heterogeneity-driving reactions that can be used as co-treatment targets or screening criteria for new therapeutics.

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QUANTITATIVE APPROACHES TO MODELLING AND ANALYSING CANCER-IMMUNE INTERACTIONS

Eszter Lakatos, Barbara Bravi

Cancer evolution is the result of the complex interplay between cancer cells and their environment, in particular the immune system. Several therapeutic approaches target this interaction, engaging the body's natural immune defences to fight cancer. However, understanding and predicting quantitatively the dynamics of immune response to cancer remains challenging.

Effective immune reaction to cancer requires (i) the presence of cancer-specific molecules (neoantigens) that can identify the cancer as "non-self", (ii) detection by specialised cells of the immune system (T-cells), and (iii) mounting an immune response initiated by the expansion of these cancer-specific T-cell. Cancer-immune co-evolution is the intricate spatio-temporal interplay and modulation of these processes. Current measurements are typically limited to the immune and neoantigen repertoires of a single time point, making it impossible to experimentally track the progression of cancer-immune interactions. Quantitative approaches provide the key to reconstructing the dynamical processes underlying static repertoire measurements. Mathematical models, calibrated on patient data, offer mechanistic insights on the joint dynamics of cancer and T-cells, and predictions at the single-patient level. In parallel, machine learning techniques have proven to be essential in characterising the signals of immune activity from cancer samples.

The aim of this mini-symposium is to bring together researchers who actively design and apply such approaches to analyse patterns of cancer-immune interactions. The talks will range from spatial and dynamical models of co-evolution to machine learning methods predicting the molecular interactions between (neo)antigens and T cell receptors. This symposium will offer the opportunity to discuss how existing quantitative approaches could be improved and fruitfully combined to better understand, predict and manipulate the immune reaction to cancer.

A HYBRID DISCRETE-CONTINUUM MODELLING APPROACH TO EXPLORE THE IMPACT OF T-CELL INFILTRATION ON ANTI-TUMOUR IMMUNE RESPONSE

Emma Leschiera (Léonard de Vinci Pôle Universitaire & Research Center, Paris La Défense, France)

Understanding the cellular processes that underlie the early stages of tumour development and tumour–immune interaction is important to guide the design of effective treatments, especially immunotherapy. For example, the infiltration of immune T cells into the tumour may

be associated with the prognosis in various types of tumours. This observation has led to the development of the"immunoscore" [1] as a prognostic marker in cancer patients. The immunoscore provides a score that increases with the density of T cells present at the center and on the edges of the tumour. In this talk, I will introduce a discrete-continuum spatial hybrid modelling approach [2] to describe the interaction dynamics between tumour cells and T cells. In this model, the dynamics of single cells (tumour and T cells) are described by an agent-based model, coupled with a partial differential equation (PDE) to describe the concentration of a chemoattractant. Such chemoattractant is secreted by tumour cells and dictates the movement of T cells towards the tumour. I will then present the continuum model that can be formally obtained from such hybrid model, which is given by a coupled system that includes an integro-differential equation for the density of tumour cells, a PDE for the density of T cells, and a PDE for the concentration of the chemoattractant. The results of computational simulations of the hybrid model will show that there is an excellent quantitative agreement between them and numerical solutions of the corresponding continuum model. These results shed light on the mechanisms that underlie the emergence of different levels of infiltration of T cells into the tumour and elucidate how T-cell infiltration shapes anti-tumour immune response. Finally, I will show the impact of T-cell infiltration on the response of tumour cells to different types of anti-cancer immunotherapy.

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PREDICTING T-CELL RECEPTOR - PEPTIDE-MHC INTERACTIONS: HOW CAN WE BRIDGE THE TWO SIDES OF THE EQUATIONS?

David Gfeller (Department of Oncology UNIL CHUV, Ludwig Institute for Cancer Research, University of Lausanne, Lausanne, Switzerland)

T cells orchestrate the adaptive immune response against pathogens and cancer by recognizing epitopes presented on MHC molecules. The heterogeneity of the MHC peptidome, including the high polymorphism of MHC genes, is influencing TCR repertoires and represents an important challenge towards accurate prediction and identification of T-cell epitopes in different individuals and different species. Here we first generated and curated a dataset of more than a million unique MHC-I and MHC-II ligands identified by mass spectrometry. This enabled us to precisely determine the binding motifs of >200 MHC alleles across several species. Analysis of these binding specificities combined with X-ray crystallography refined our understanding of the molecular determinants of MHC motifs and revealed alternative binding modes of MHC ligands. We then developed a machine learning framework to accurately predict binding specificities and ligands of any MHC allele (MixMHC(2)pred), and further integrated TCR

recognition into our epitope prediction pipeline (PRIME). In parallel, we developed a machine learning pipeline (MixTCRpred) to predict which TCRs can recognise some of these epitopes. Prospectively application of PRIME to SARS-CoV-2 proteins identified several epitopes and analysis of TCR repertoires of COVID-19 patients with MixTCRpred revealed enrichment of clonotypes predicted to bind an immunodominant SARS-Cov-2 epitope. Overall, our work shows how in depth characterization of MHC motifs and TCR specificities can help understanding and predicting TCR epitope recognition.

INDIVIDUAL-BASED MODELLING OF THE INTERACTION BETWEEN CANCER AND T CELLS IN VITRO: AN INVESTIGATION OF THE ROLE OF METABOLIC REPROGRAMMING OF CANCER CELLS AND THE EFFECTS OF T CELL EXHAUSTION

Tomás Alarcón (Centre de Recerca Matemàtica, Bellaterra, Barcelona, Spain)

The development of immuno-therapeutic agents, such as anti-checkpoint drugs, has opened new avenues in cancer therapy. Despite the initial enthusiasm regarding these treatments, more detailed studies and clinical trials have revealed that the response to these treatments exhibits a considerable degree of heterogeneity. Specifically, while in many cases resistance ensues, many others are simply not responsive. As a way to tackle this situation we present computational and experimental investigations of the interaction between cancer cells and activated T cells in vitro. We investigate the effects of metabolic reprogramming of the cancer cells in order to make them more responsive to the T cells. Furthermore, we use our mathematical model to explore the role of T cell exhaustion and antigen levels.

IMMUNE EVASION IMPACTS THE LANDSCAPE OF DRIVER GENES DURING CANCER EVOLUTION

Luis Zapata Ortiz (Centre for Evolution and Cancer, The Institute of Cancer Research, London, UK)

Carcinogenesis is driven by interactions between genetic mutations and the local microenvironment. Recent research has identified hundreds of cancer driver genes; however, these studies often include a mixture of different molecular subtypes and ecological niches and ignore the impact of the immune system. Here, we explored the impact of immune evasion on the landscape of driver genes and the prognosis of these tumors in the clinic. We analyzed 9,896 primary tumors from The Cancer Genome Atlas using the ratio of non-synonymous to synonymous mutations (dN/dS) and found 27 novel driver genes. The dN/dS of driver genes in escaped tumors

was significantly lower and closer to neutrality than in non-escaped tumors, suggesting selection buffering in driver genes fueled by immune escape. Additionally, we found that immune evasion leads to more mutated sites, a diverse array of mutational signatures and is linked to tumor prognosis. Moreover, we found that escaped tumors respond better to immunotherapies due to their accumulation of neoantigens pre-treatment. Despite the selective advantage of immune evasion, we also found that it is a late event during carcinogenesis often associated with inflammation. Our findings highlight the need for improved patient stratification based on genomic data to identify new therapeutic targets for cancer treatment.

A DYNAMICAL MODEL OF PD-1/PD-L1 AND CTLA-4 IMMUNE-CHECKPOINT THERAPY

Kamran Kaveh (Department of Applied Mathematics, University of Washington, Seattle, WA, USA)

Immune checkpoint therapy is one of the most promising immunotherapeutic methods that are likely able to give rise to durable treatment response for various cancer types. Despite much progress in the past decade, there are still critical open questions with particular regards to quantifying and predicting the efficacy of treatment and potential optimal regimens for combining different immune-checkpoint blockades. To shed light on this issue, here we develop clinically-relevant, dynamical systems models of cancer immunotherapy with a focus on the immune checkpoint PD-1/PD-L1 blockades as well as CTLA4. Our model allows the acquisition of adaptive immune resistance in the absence of treatment, whereas immune checkpoint blockades can reverse such resistance and boost anti-tumor activities of effector cells. We develop a predictive model for CTLA4 and PD-1 combination therapy and compare/validate the results with existing patient data and in-vivo models. Our modeling framework lays the ground for future data-driven analysis on combination therapeutics of immune- checkpoint treatment regimes and thorough investigation of optimized treatment on a patient-by-patient basis. Finally, we propose a relationship between neoantigenic distribution derived from an evolutionary process during cancer progression, and the dynamical response to immune-checkpoint therapies. Our results show when tumor mutational burden (TMB) is a good determinant of treatment response and when it is not.

STOCHASTIC MUTATION RATE SWITCHING IN RESPONSE TO IMMUNE SELECTION IN MISMATCH REPAIR-DEFICIENT COLORECTAL CANCER (MMRD CRC)

Lauren McKenzie (Department of Pathology, UCL Cancer Institute, University College London, London, UK)

Background: Cancer is a genetic disease caused by mutations in our DNA. Disruption of pathways responsible for maintaining genomic integrity significantly increases cancer risk, with 15% of CRCs arising from dysfunctional MMR. Extensive mutational damage in these lesions accelerates tumour growth but also increases neoantigen burden, rendering them vulnerable to attack by the immune system. Understanding how MMRd tumours fine-tune their evolutionary tempo to balance evolvability against immune recognition may give insight into why 50% of MMRd CRC patients do not respond to immunotherapy, despite their increased immunogenicity. Our recent work has uncovered a novel mechanism whereby coding homopolymers in the DNA repair genes, MSH3 and MSH6, are repurposed by MMRd tumours to act as evolvability switches. Spontaneous mutation and reversion within these repetitive tracts allow tumour subclones to successfully navigate immune adaptation whilst minimising the deleterious impact of prolonged genomic hypermutation. This mirrors the mechanism where hypermutable loci are exploited by bacterial species to facilitate rapid phenotypic acclimation in response to environmental pressures.

Methodology: Ongoing research to further explore mutation rate switching includes WGS of spatially disparate LCM-captured MSH3/6-proficient and -deficient clones, as well as a comprehensive library of MMRd CRISPR cell models. These complementary datasets will permit in-depth comparison of genomic mutation rates, mutation distribution, and clonal diversity between subclones at monophyletic resolution. Additional work establishing PDO and PBMC co-cultures will be used to study the functional consequences of tumour and immune cell interaction. Data from these parallel experiments will provide novel insight into the evolutionary trajectories MMRd lesions take in response to immune selection, and may produce valuable clinical markers to broaden the scope of patients who benefit from immunotherapy.

MODELING THE CO-EVOLUTION OF AN EVOLVING CANCER AND T CELL REPERTOIRE: CHALLENGES AND EXCITING OPPORTUNITIES FOR MATHEMATICS TO IMPROVE T CELL IMMUNOTHERAPY

Jason T. George (Department of Biomedical Engineering, Texas A&M University, College Station, TX, USA)

The adaptive immune system contains an extraordinary number ($\sim$109) of unique T cells, each capable of recognizing and killing malignant cells through the recognition of 9- to 11-amino acid tumor-associated antigens present on the cell surface. The size of allowable T cells

(by some estimates 1020) and number of possible antigens (1013) preclude a comprehensive experimental analysis of the problem. While daunting, this complexity invites the development of analytical and numerical mathematical approaches. In this talk I will discuss our efforts to understand this general problem by taking two distinct directions. First, I will discuss how stochastic modeling can be used to relate observable cancer incidence and immunotherapeutic efficacy to immune escape. In the remaining time, I will present recent attempts to develop biophysically trained models for predicting favorable T cell-antigen interactions.

THE INTERPLAY BETWEEN THE CANCER CELL AND THE IMMUNE MICROENVIRONMENT DURING CANCER EVOLUTION

Nicholas McGranahan (Department of Oncology, UCL Cancer Institute, University College London, London, UK)

Emerging data have highlighted the importance of considering cancer evolution in the context of a predatory immune microenvironment. Key mediators of a cytotoxic immune response in cancer are neoantigens, which are cancer cell-specific alterations that result in mutant peptides capable of eliciting a T cell-mediated, human leukocyte antigen (HLA)-restricted, immune response. Crucially, a mutation can only result in a neoantigen if the associated mutant peptide is presented on HLA molecules to the T cell receptor. In this talk I will outline our methods which seek to evaluate and quantify the levels of circulating and infiltrating immune cells, as well as our tools which we use to explore both genetic and non-genetic mechanisms of disruption of HLA presentation. Together, this work will provide an overview of the complex interplay between the cancer cell and the immune microenvironment during cancer evolution.

MODELING AND ANALYSIS IN CELL BIOLOGY: MULTI-SCALE PERSPECTIVES

Martina Conte, Romina Travaglini

The biology of cell evolution is characterized by an inherent multi-scale nature, as it involves several mechanisms occurring at different spatial and temporal scales. Such mechanisms range from molecular intra-cellular processes (at the subcellular scale) to local inter-cellular interactions (at the cell scale), and these last ones are further interlinked to the collective population dynamics (at the tissue scale). For instance, cell motion relies on several factors, varying from single cell-adhesion properties and cell polarisation dynamics, to tactic collective migration toward target sites. Analogously, in the studies on drug efficacy, a proper interplay between the fast timescale of chemical evolution and the slow timescale of cell dynamics influence is critical for optimal treatment strategies. Understanding the complex interconnections among these phenomena remains a great challenge of modern bioscience. On the one hand, developing mathematical frameworks handling different scales is a key ingredient for more accurate and complete modeling. On the other hand, the formulation and analysis of these models require sophisticated techniques. These could involve derivation and study of ordinary or partial differential equations, stability, and patterning analysis, as well as optimal control theory. This complexity leads also to a series of analytical and numerical challenges, making them interesting mathematical objects per se. This mini-symposium aims to present recent applications of mathematical models in cell biology proposed in the spirit of a multi-scale approach, demonstrating their relevance for both the mathematical analysis itself and the description of real phenomena. We bring together researchers from different countries and at different stages of their academic careers to illustrate the most recent advancements in their fields.

MODELING NON-LOCAL CELL-CELL ADHESION: A MULTI-SCALE APPROACH

Anna Zhigun (Mathematical Sciences Research Centre - Queen's University Belfast)
Other authors: M. L. Rajendran

Cell-cell adhesion plays a vital role in the development and maintenance of multicellular organisms. In cancer, one of its functions is the regulation of cell migration. In this talk, a versatile multiscale approach to modelling a moving self-adhesive cell population will be presented that combines a careful microscopic description of a deterministic adhesion-driven motion component with an efficient mesoscopic representation of a stochastic velocity-jump process. This approach gives rise to mesoscopic models in the form of kinetic transport equations featuring

multiple non-localities. Subsequent upscaling produces general classes of equations with non-local adhesion and myopic diffusion. Cell-cell adhesion relies on binding of the cell adhesion molecules, such as, e.g. cadherins. Our approach lends itself conveniently to capturing this microscopic effect. On the macroscale, this results in an additional non-linear integral equation of a novel type that is coupled to the cell density equation.

DIFFUSION-DRIVEN INSTABILITY IN BULK-SURFACE REACTION-DIFFUSION SYSTEMS

Davide Cusseddu (CMAT - Universidade do Minho)

Systems of coupled bulk and surface equations model the interactions between quantities defined over 3 and 2-dimensional spaces. These constitute a particularly useful mathematical framework in many different modeling scenarios. One example is constituted by protein interactions between the cell membrane and the cell interior. For instance, during cell polarisation, certain proteins tend to accumulate over specific areas of the cell membrane, breaking the cell symmetry and giving rise to spatial patterns. In this talk, I will present and discuss different examples of surface patterning in bulk-surface reaction-diffusion systems. A particular interest will be dedicated to the analysis of conditions inducing diffusion-driven instability in the solutions. In particular, I will discuss minimality assumptions for the appearance of Turing-like patterns in such systems. After touching upon the numerical method used for solving such systems, I will present some numerical solutions over different 3-dimensional geometries.

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A LINEAR OPTIMAL CONTROL MODEL OF IMMUNOTHERAPY FOR RECURRENT AUTOIMMUNE DISEASE

Kamilia Azib (CMAT - Universidade do Minho)
Other authors: M. da Piedade Ramos, C. Ribeiro

In this work, we develop a mathematical model describing the impact of drug therapies on recurrent autoimmune disease. We describe the immune system interactions at the macroscopic level of self-antigen presenting cells, self-reactive T cells, immunosuppressive cells, and Interleukin-2 (IL-2) cytokines. The drug therapy consists of an intake of Interleukin-2 cytokines which boosts the effect of immunosuppressive cells on the autoimmune reaction. We derive macro-analogies and demonstrate the positivity and well-posedness of the solution. We then examine the equilibrium of the corresponding dynamical system and its stability. By applying dynamical system theory, we show that continuous oscillations occur when a Hopf bifurcation occurs. We formulate an optimal control problem relative to the model so that the quantity of both the self-reactive T cells that are produced in the body and the Interleukin-2 cytokines that are administrated is simultaneously minimized. Moreover, we perform some numerical tests in order to investigate optimal treatment strategies and the results reveal that the optimal control approach provides good-quality approximate solutions and shows to be a valuable procedure in identifying optimal treatment strategies.

A COMPUTATIONAL MULTI-SCALE APPROACH TO THE THERAPEUTIC RESISTANCE OF PROSTATE CANCER

Marianna Cerasuolo (Department of Mathematics, University of Sussex, UK)
Other authors: A. Burbanks, R. Ronca, A. Ligresti

Androgen deprivation therapy is the first line of treatment for prostate cancer. However, a majority of patients eventually progress to a refractory state, leading to castration-resistant prostate cancer (CRPC). Recently, second-generation drugs and their combinations have received approval for CRPC treatment. Despite this, there are reported cases of tumors resisting these new drugs. Over the past few years, numerous mathematical models have been proposed to describe the dynamics of prostate cancer during treatment. One of the predominant challenges has been accurately representing experiments conducted under in vivo conditions, as this is crucial for the models' suitability in clinical applications (see, for example, [1, 2]). This talk will present an interdisciplinary study on drug resistance in prostate cancer. We will show how, by integrating experimental data, statistical analysis, and computational methods, we could devise potential therapeutic strategies to address drug resistance. The proposed models explore neuroendocrine transdifferentiation in prostate cancer in vivo under multiple drug therapies and account for the heterogeneity of the tumor microenvironment. As the behaviors of the prostate cancer cells and the various chemicals occur on different time scales, we considered a multi-scale hybrid approach, in which partial differential equations govern the behavior of the drugs and other chemicals present in the tumor microenvironment (over the 'fast' timescale); and a cellular automaton provides the rules for the dynamics of the tumor cells (over the 'slow' timescale). We will see how, through the computational analysis of the model solutions, it was possible to examine the spatial dynamics of tumor cells, assess the efficacy of various drug therapies in inhibiting prostate cancer growth, and optimal drug combination strategies and treatment schedules to eradicate cancer cells and prevent metastases formation.

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NEW DIRECTIONS FOR STOCHASTIC MODELS OF EPIDEMICS

Jacob Curran-Sebastian, Thomas House

Stochastic models of epidemics have a rich history in the field alongside better-known deterministic differential equation approaches. As well as improving insights into the theory of disease transmission and analysis of infectious disease data, these models and their analysis have stimulated research in probability and computational methodology. Some of the earliest approaches to stochastic models were discrete-time Markov processes such as the chain binomial model and, since then, a large number of processes in continuous and discrete time including branching processes, diffusions, non-Markovian processes, renewal processes, non-linear Markov processes, hybrid models, and many more.

This symposium seeks to explore some of the exciting new directions in this area. These include modelling outbreaks using a variety of the stochastic processes mentioned above, such as birth-death and Hawkes processes, which yield insights on disease dynamics in low-prevalence settings. We will also discuss the impact of changes and heterogeneities in the population, including in environments where the susceptible population is growing, or when interventions are limited by the availability of resources. Further heterogeneities are also considered, such as by modeling a network or age structure on the population, which affect the long-term dynamics of an epidemic. These talks will further address modelling at different scales including, for example, different spatial scales and at the within-host level. Finally, this symposium will contain approaches for fitting these models to outbreak data, such as via the use of hierarchical Bayesian models, which ensure principled epidemic forecasting and realistic assessment of the impact of interventions.

In addition to hearing talks from a diverse set of speakers on these topics, we hope that the symposium will allow all participants opportunities to interact and cross-pollinate new scientific concepts in this exciting area.

USING HAWKES PROCESS TO MODEL MALARIA IN COUNTRIES CLOSE TO ELIMINATION

Juliette Unwin (University of Bristol, UK)
Other authors: K. Wangdi, S. Bhatt

Globally there were an estimated 249 million malaria cases and 608,000 malaria deaths in 85 countries during 2022, predominantly in Africa, with 34 countries reporting fewer than 1000 locally acquired cases of the disease (https://www.who.int/publications/i/item/9789240064898).

This has increased from just 13 countries in 2000 and with careful monitoring and surveillance, elimination may now be possible in these 34 countries.

Modelling malaria in low transmission settings is challenging because prohibitively large sample sizes are needed to use traditional gold standard measures such as parasite prevalence. Instead, we propose using a self-exciting point process known as Hawkes Processes to capture malaria disease dynamics in countries that are close to eliminating malaria. These processes consist of two components: a background term that represents imported cases and a kernel that captures person to person transmission through the mosquito vector. Our model combines malaria specific information, such as the shape of the infectious profile, within a rigorous statistical framework to fit incidence data.

In initial work, we show that not only is it possible to accurately recreate the case counts over time with our Hawkes Process method, but it is possible to accurately predict the proportion of cases that are imported [1]. We also show that this model is robust to some missing cases in the incidence data. In ongoing research, we are extending this method to better capture Plasmodium vivax malaria instead of the more common Plasmodium falciparum malaria and thinking how to extend the kernel to encode other data sources such as space that are routinely collected at the health clinics.

[1] Unwin, H. J. T. et al. (2021). Using Hawkes Processes to model imported and local malaria cases in near-elimination settings. PLOS Computational Biology, 17(4), e1008830. https://doi.org/10.1371/journal.pcbi.1008830

STOCHASTIC ANALYSIS OF AN EPIDEMIC MODEL IN A RESOURCE-LIMITED ENVIRONMENT

Antonio Gómez-Corral (Complutense University of Madrid, Spain)
Other authors: MJ. Lopez-Herrero, D. Taipe

In this contribution we present a Markov chain model to study how a pathogen spreads among a finite number of individuals within a population in a resource-limited environment. The assumption that only a limited number of infectives can receive medical care—once they are isolated in a hospital ward from the sub-population of non-isolated susceptible and infected individuals—leads us to distinguish between the epidemic that develops inside the hospital ward and the spread of the pathogen outside, in such a way that the resulting models can be seen as of SIS-type and of SI-type, and they are inherently linked to each other. Our aim is to study the influence of the resource-limited environment on performance measures related to hospital operations or the economic impact of administering therapeutic treatments. The talk is mainly based on our recent work in [1, 2].

[1] Gómez-Corral, A., Lopez-Herrero, M.J., Taipe, D. (2023). A Markovian epidemic model in a resource-limited environment. Applied Mathematics and Computation, 458, 128252. https://doi.org/10.1016/j.amc.2023.128252

A BAYESIAN SEIR MODELING APPROACH TO QUANTIFYING THE IMPACT OF COVID-19 VACCINATION ON LIVES SAVED IN SWEDEN 2021

Fanny Bergström (Stockholm University, Sweden)
Other authors: T. Britton

A mathematical model is employed to analyze the impact of COVID-19 vaccination on lives saved in Sweden during 2021. Utilizing real-world data on COVID-19 incidence, vaccination coverage, and demographic variables, the Susceptible-Exposed-Infectious-Removed (SEIR) model captures the dynamic interplay among susceptible, exposed, infectious, and removed individuals, offering insights into the trajectory of the pandemic. A Bayesian framework is applied to account for uncertainties in parameter estimates, providing a robust foundation for assessment.

By incorporating estimated vaccination-related parameters, age-specific infection-fatality-ratio (IFR) and underreporting, our model facilitates the estimation of lives saved attributable to COVID-19 vaccines. The results not only emphasize the direct impact of vaccination on reducing severe outcomes but also shed light on potential indirect effects on transmission dynamics.

This research contributes to the growing body of literature focused on quantifying the real-world impact of COVID-19 vaccination. The Bayesian SEIR model presents a flexible and data-driven framework, empowering decision-makers to assess the effectiveness of vaccination strategies.

[1] Bergström, Fanny et al. (2022). Bayesian nowcasting with leading indicators applied to COVID-19 fatalities in Sweden. PLOS Computational Biology, 18(12), e1010767. https://doi.org/10.1371/journal.pcbi.1010767

MODELLING SPREADING ON NETWORKS

James Gleeson (University of Limerick)

Network models may be applied to describe many complex systems, including contact networks for disease transmission. In the era of online social networks the study of dynamics on networks is also an important branch of computational social science. In this talk I will review some stochastic models for spreading processes that occur on the nodes of a network and consider their relation to compartmental models in epidemiology.

[1] Gleeson, J. P., Durrett, R. (2017). Temporal profiles of avalanches on networks. Nature Communications, 8(1). https://doi.org/10.1038/s41467-017-01212-0
[2] Gleeson, J. P. et al. (2021). Branching process descriptions of information cascades on

Twitter. Journal of Complex Networks, 8(6). https://doi.org/10.1093/comnet/cnab002

TIME SERIES MODELS OF EPIDEMICS AND ASSOCIATED TREE STRUCTURES

Niket Thakkar (Institute for Disease Modeling, Global Health, Bill and Melinda Gates Foundation, Seattle, US)
Other authors: M. Famulare

In this talk we show that widely used compartmental disease models can be reinterpreted as interacting collections of branching processes, individually representing transmission trees but grown to capture the epidemiology in aggregate. We call this stochastic process a transmission forest. Taking this perspective to COVID-19 time series from Washington State from January 2020 to March 2021, we demonstrate that the transmission forest is an intuitive platform for estimating transmission's higher order statistics, like the clustering of cases as outbreaks. This allows us to make predictions which we find to be consistent with related observations from contact tracing and outbreak investigation.

Then, leveraging ideas from analytic combinatorics, we develop a mathematical theory of forest statistics, leading to direct calculations of the size distribution and survival properties of transmission trees based on time series data alone. This detailed, quantitative understanding of the tree distribution gives insight into Washington's genetic sequence data and the geometric structure of the phylogenetic tree. Finally, looking ahead, we discuss some mathematical questions associated with the transmission forest's subgraphs. Recent work on these problems points towards new applications on open, heterogeneous transmission systems and other respiratory pathogens.

LONG-TERM BEHAVIOUR OF A STOCHASTIC EPIDEMIC IN A GROWING POPULATION

Malwina Luczak (The University of Manchester, UK)
Other authors: G. Brightwell

We study a model of an epidemic in a growing population, introduced by Britton and Trapman (2014). The population is modelled as a supercritical linear birth-and-death process, and the epidemic model in a standard SIR process. Britton and Trapman (2014) conjectured that, in the regime where the epidemic may become endemic in the population, the proportions of infectives, susceptibles and recovered converge to the unique attractive fixed point of a certain differential equation. We prove this conjecture, and also provide a broader picture of the trajectory of the scaled epidemic process as it converges to the fixed point. This presentation is

based on a preprint joint with Graham Brightwell.

APPLICATIONS OF BAYESIAN STOCHASTIC HIERARCHICAL MODELS IN EPIDEMIOLOGY

Punya Alahakoon (The University of Melbourne, Australia, University of New South Wales, Australia)
Other authors: P. G. Taylor, J.M. McCaw

We consider infectious disease outbreaks that evolve in isolation without the influence of one another. Standard approaches to Bayesian hierarchical analysis, when outbreaks are modelled as stochastic processes, can be computationally prohibitive. However, we have introduced a novel algorithm that allows efficient parameter estimation within such frameworks. By extending this work, I will demonstrate how various insights into multiple outbreaks can be obtained through hierarchical analyses with datasets from the 1918 influenza and COVID-19 pandemics. The Australian Quarantine Service was established during the 1918-19 influenza pandemic. Consequently, vessels were required to record infections on board. When returning to Australia, they were intercepted; and individuals were examined and quarantined. We studied such outbreaks that occurred on board ships in late 1918. By taking a stochastic Bayesian hierarchical modeling approach to estimate key epidemiological parameters, I will show that the use of Quarantine Stations provided varied benefits and depended on the epidemiological status of the ship at the time of quarantine. In the second study, we studied the spread of SARS-CoV-2 across rural counties in North and South Dakota, United States before the introduction of the delta variant. Similar to our previous study, I will demonstrate how a stochastic Bayesian hierarchical framework can be used to analyse this dataset. Furthermore, I will show how this estimation framework was useful to characterise the effects of non-pharmaceutical interventions implemented at the time.

[1] Alahakoon, P., McCaw, J. M., Taylor, Peter G. (2022). Estimation of the probability of epidemic fade-out from multiple outbreak data. Epidemics, 38, 100539.
https://doi.org/10.1016/j.epidem.2022.100539
[2] Alahakoon, P., Taylor, P. G., McCaw, J. M. (2023). How effective were Australian Quarantine Stations in mitigating transmission aboard ships during the influenza pandemic of 1918-19?. PLOS Computational Biology, 19(11), e1011656.
https://doi.org/10.1371/journal.pcbi.1011656

MODELING THE IMPACT OF HUMAN MOVEMENT ON THE SPREAD OF DENGUE VIRUS: THE IMPORTANCE OF APPROPRIATE SPATIAL SCALES

Alun Lloyd (Biomathematics Graduate Program and Department of Mathematics, North Carolina State University)
Other authors: A. Black, A. Smith, J. Ross

In this talk we discuss a number of modeling frameworks (from multi-patch mathematical models to individual-based simulation models) for analyzing the impact of human movement on the spread of dengue virus. Despite their attractiveness—due to their mathematical tractability—and widespread use, we demonstrate limitations of multi-patch models. We show that household based models, a tool with a long history of use for directly-transmitted infections, can provide an analytically-tractable tool to supplement the use of large-scale computational models.

RECENT ADVANCES IN MODELLING CANCER INVASION

Chiara Villa, Tommaso Lorenzi

Tumor invasion is a crucial step in the metastatic cascade of solid tumors, with serious consequences for disease progression. At this stage the tumor leaves the in-situ and often benign stage to become more aggressive. Tumor invasion is characterized by a very large number of bio-physical and bio-chemical effects. Indeed, tumor cells need to breach and move through a dense mesh of extra-cellular matrix fibers, thus generating stress, and pro-tumor cells of the micro-environment secrete enzymes used as directional cues or tools to perform invasion. Mathematical models of cancer invasion can help biologists to better understand this phenomenon by testing hypotheses in-silico, and provide a flexible framework that can be used to investigate new therapeutic strategies. Over the years, a wide variety of mathematical models have been proposed to systematically assess the mechanisms responsible for cancer invasion, and this biomedical problem has been a prolific source of mathematical questions. We propose a mini symposium to catch up with recent advances in modelling cancer invasion, from stochastic to deterministic approaches, from microscopic to macroscopic scales.

PROLIFERATION-IMMUNO-EVASION TRADE-OFF: A CONTINUOUS MODEL FOR TUMOR-IMMUNE DYNAMICS AND THERAPEUTIC STRATEGIES

Giulia Chiari (Politecnico di Torino, Università di Torino, Swinburne University of Technology)
Other authors: J.A. Carrillo, M. E. Delitala.

We propose a continuous model capturing the interplay between tumor mass and the immune system, grounded in the assumption of proliferation-immuno-evasion trade-off. Inspired by [1], we adapt their model, introduced to reproduce geometric configurations and invasion fronts of a co-colture experiments, incorporating a nonlocal attraction formulation for adhesion and chemoattraction forces at the microscopic level. In our model, tumor cells exhibit Fisher-type proliferation, slow diffusive motion, and an internal cohesive force ensuring mass formation. Immune cells display strong diffusion and an attraction toward tumor cells. Cancer cells with an epigenetic signature promoting fast reproduction are more visible (attract immune cells with a stronger kernel) and neutralizable (high killing rate). Conversely, low proliferative cells may achieve immuno-invisibility and resistance. The model aims to explore how this trade-off influences immune interventions on tumor mass and the outcome for their evolution. We refer to [2], where tumors are classified based on T-cell infiltration and temperature (hot/cold

tumors), which is an indicator of the inflammatory state. Initially, homogeneous tumor populations with a single epigenetic signature are analyzed, assessing the impact of population characteristics. Subsequently, heterogeneous populations with two subpopulations of distinct epigenetic traits are considered, evaluating effects of quantitative (percentage of total mass for each subpopulation) and geometric composition (location of cell types). Finally, an epigenetically structured model is introduced, employing a continuous epigenetic variable to capture mass composition heterogeneity. This approach provides insights into diverse tumor-immune scenarios, aiding the understanding of therapeutic strategies.

[1] Carrillo, J.A. et al. (2019). A population dynamics model of cell-cell adhesion incorporating population pressure and density saturation. Journal of Theoretical Biology, 474, 14-24. https://doi.org/10.1016/j.jtbi.2019.04.023

MULTISCALE MODELLING OF GLIOMA INVASION UNDER THE INFLUENCE OF THE MICROENVIRONMENT

Martina Conte (Politecnico di Torino)

Glioma is the most prevalent, aggressive, and invasive subtype of primary brain cancer, characterized by rapid cell proliferation and great infiltration capacity. Its growth and migration inside the brain is a highly complex phenomenon, influenced by a multitude of intrinsic and extrinsic factors. Although research advances have allowed significant progress in the comprehension and treatment of gliomas, their infiltrative spread strongly relates to poor patient survival prognosis. Here, we propose a mathematical framework for the description of tumor invasion and progression into the healthy tissue in response to different microenvironmental factors. Cell dynamics are modeled with a multilevel description that starts from the individual level, accounting for single-cell dynamics, and integrates them into a mesoscopic level, whose corresponding macroscopic limit leads to the evolutionary equation for the macroscopic cell density. The derived setting is numerically then tested in several scenarios with the main aim of showing tumor response to different microenvironmental changes.

[1] Conte, M., Surulescu, C. (2021). Mathematical modeling of glioma invasion: acid- and vasculature mediated go-or-grow dichotomy and the influence of tissue anisotropy. Applied Mathematics and Computation, 407, 126305. https://doi.org/10.1016/j.amc.2021.126305
[2] Conte, M. et al. (2023). Mathematical modeling of glioma invasion and therapy approaches via kinetic theory of active particles. Mathematical Models and Methods in Applied Sciences, 33(05), 1009-1051. https://doi.org/10.1142/S0218202523500227

TRAVELLING WAVES IN HETEROGENEOUS CELL POPULATIONS

Rebecca Crossley (University of Oxford)
Other authors: K. Painter, T. Lorenzi, P. Maini, R. Baker.

Collective cell motility is a widely observed phenomenon in many biological scenarios, from early development to tumour growth. A range of modelling approaches have been employed to study this, that often do not consider population heterogeneity, which is associated with treatment failure and the recurrence of cancer.

In this work, we compare a model for a homogeneous population of cells to a heterogeneous population comprising two sub-populations of specialist cells that can either move or proliferate, in line with the 'go-or-grow' hypothesis. We explore how different hypothetical phenotypic switching functions impact the speed and structure of the invading cell populations, and contrast this to similar results for the homogeneous population of cells. Beyond providing insight into the qualitative behaviour of cell invasion models with phenotypic structuring, the results we present could also be used to infer the underlying mechanisms governing collective cell migration that could aid the developments of future cancer treatments.

[1] Crossley, R.M. et al. (2023). Traveling waves in a coarse-grained model of volume-filling cell invasion: Simulations and comparisons. Studies in Applied Mathematics, 151(4), 1471-1497. https://doi.org/10.1111/sapm.12635
[2] Crossley, R.M. et al. (2024).Phenotypic switching mechanisms determine the structure of cell migration into extracellular matrix under the 'go-or-grow' hypothesis. arXiv. https://doi.org/10.48550/arXiv.2401.07279

HYBRID MODELLING FOR CANCER INVASION AND METASTASIS

Dimitrios Katsaounis (University of St Andrews)

Cancer cells have the ability to interact with the tumour microenvironment and invade the surrounding tissue by reformulating the extracellular matrix (ECM). The coordinated actions of cancer cells, the ECM, cancer associated fibroblasts (CAFs), and the epithelial to mesenchymal transition (EMT) result to in the invasion of the tissue. In this work a multiscale hybrid mathematical model is proposed, which combines the macroscopic nature of the phenomenon, where solid tumours of epithelial-like cancer cells (ECCs) invade the tissue, as well as the microscopic individual based strategies of mesenchymal-like cancer cells (MCCs). The model consists of partial and stochastic differential equations that describe the evolution of the ECCs and the MCCs while accounting for the transitions between the two phenotypes. Numerical simulations of the proposed model capture the heterogenous nature of cancer invasion and metastasis, where we observe simultaneously the growth of the solid body of the tumour and the creation of cancer islands by the MCCs away from the initial location. We extend our

numerical simulations to a multi-organ framework where the individual cancer cells, active in a primary tissue, enter the vasculature network, arrive in different organs and create smaller metastases.

[1] Katsaounis, D. et al. (2024). A genuinely hybrid, multiscale 3D cancer invasion and metastasis modelling framework. bioRxiv. https://doi.org/10.1101/2024.01.12.575361

INSIGHTS AND EMERGING TRENDS IN INFECTIOUS DISEASE MODELING AND MATHEMATICAL ANALYSIS

Burcu Gürbüz, Alan D. Rendall

Mathematical models play a crucial role in informing public health decisions related to disease spreading. Accurately predicting transmission and the temporal evolution of viral diseases presents a significant challenge in light of complicating factors such as population heterogeneity, mobility, vaccination strategies, subpopulations with underlying conditions, and differentiation of the virus into multiple strains with varying levels of infectiousness. The mini-symposium aims to provide a contribution to the investigation of dynamical systems in mathematical biology that emphasizes rigorous mathematical analysis and disease modeling. It will also include analysis across multiple scales from within-host to population level. Researchers and practitioners are encouraged to submit their contributions to enhance understanding of these systems, with emphasis on mathematical modeling, data fitting, and qualitative analysis. The mini-symposium will explore the dynamic field of mathematical biology and foster collaboration amongst applied mathematicians, biologists, and medical professionals in bridging the gap between theoretical insights and practical applications in the field.

IMITATION DYNAMICS OF VACCINATION WITH DISTRIBUTED DELAY RISK PERCEPTION

Yuliya Kyrychko (University of Sussex, United Kingdom)
Other authors: K. Blyuss.

In this talk I will discuss the dynamics of paediatric vaccination when modelled as a game, where increase in the rate of vaccination is taken to be proportional to the perceived payoff. Similarly to earlier models, this payoff is considered to be a difference between the perceived risk of disease, as represented by its momentary incidence, whereas for the perceived risk of vaccine side effects I will use an integral of the proportion being vaccinated with some delay kernel. This delay distribution can model two realistic effects: the fact that vaccine side effects take some time to develop after a person has been vaccinated, and that even after side effects have appeared, awareness of them will continue to impact vaccination choices for some period of time. I will discuss conditions of feasibility and stability of the disease-free and endemic steady states of the model for the general delay distribution, and for some specific delay distributions that include discrete delay, Gamma distribution (weak and strong cases), and the acquisition-fading kernel. By computing bifurcation diagram of the endemic equilibrium we are able to establish parameter regions, where some steady level of infection is maintained, as well

as regions where periodic solutions around the endemic steady state are observed. I will present a comparison of stability regions for endemic steady state, highlighting differences between distributions that are observed for the same values of parameters. This will demonstrate that not just the mean time delay, but also the details of the distribution are important when analysing the dynamics. To make the model more realistic, I will also consider the impact of a public health campaign on vaccination dynamics and contrast it to the case where vaccination choices are only dictated by information exchange between vaccinating and non-vaccinating people.

[1] Kyrychko, Y. N., Blyuss, K. B. (2023). Vaccination games and imitation dynamics with memory. Chaos: An Interdisciplinary Journal of Nonlinear Science, 33(3). https://doi.org/10.1063/5.0143184

THE PROBLEM OF VIABILITY IN MATHEMATICAL EPIDEMIOLOGY

Peter Rashkov (Bulgarian Academy of Sciences, Bulgaria)

Continuous-time deterministic compartmental mathematical models are often used to simulate and analyze the course of epidemic outbreaks in time [1]. Whereas modelling of control measures in the context of mathematical epidemiology has focused on optimal resource allocation, an important problem is the study of transient dynamic behaviour under state and input constraints for the dynamical system. These constraints normally reflect limitations in the intervention measures due to budget, capacity of healthcare system, or public policy goals. Rigorously speaking, we address the problem of viability or existence of solutions of the controlled dynamical system that share a given set of properties, namely such solutions that respect a given upper bound on the phase variable (the size of the infected host compartment) whenever the control takes values in a given bounded compact set. Our goal is to characterise the system's viability kernel, or the set of those initial states of the dynamical system such that solutions of the controlled system remain viable with respect to the given constrains for all future time. The viability kernel can be defined in several ways, but we focus on a level-set approach [2,3] based on value functions satisfying a dynamic programming principle, whereby kernels with positive Lebesgue measure can be approximated numerically. In some special situations, it can be characterised explicitly. Examples are provided in the context of one- and two-patch models for a vector-borne disease.

[1] Kooi, B. W., Rashkov, P., Venturino, E. (2023). Multi-Strain Host-Vector Dengue Modeling: Dynamics and Control. Bio-mathematics, Statistics, and Nano-Technologies, 110-142. https://doi.org/10.1201/9781003035992-6
[2] Rashkov, P. (2022). Modeling repellent-based interventions for control of vector-borne diseases with constraints on extent and duration. Mathematical Biosciences and Engineering , 19(4):4038-4061. https://doi.org/10.3934/mbe.2022185
[3] Rashkov, P. (2021). A model for a vector-borne disease with control based on mosquito repellents: A viability analysis. Journal of Mathematical Analysis and Applications, 498(1),

124958. https://doi.org/10.1016/j.jmaa.2021.124958

WAITING FOR THE PERFECT VACCINE

Gergely Röst (University of Szeged, Hungary)
Other authors: Z. Wang, S. M. Moghadas.

Vaccination has proven to be the most effective public health measure in the fight against various infectious diseases. For emerging or re-emerging diseases, a highly efficacious vaccine may not be available at the start of an outbreak. Timelines for availability of a safe and effective vaccine may significantly affect disease dynamics, its burden, and the healthcare resource utilization. Mitigating this impact may then rely on low-efficacy vaccines that may be rapidly produced and distributed to at-risk populations at the early stages of an outbreak. With the expectation for arrival of a more effective vaccine at a later stage of the outbreak, the optimal vaccination coverage with the existing, low-efficacy vaccines is elusive. While flattening the outbreak if a significant proportion of the susceptible population is vaccinated with a low-efficacy vaccine, the overall infections may not be minimized if a small proportion of the population left unvaccinated when a highly efficacious vaccine becomes available. The optimal coverage for early vaccination could thus depend on several parameters including the efficacy of the currently available vaccines, arrival timing of a more effective vaccine and its efficacy, and the transmissbility of the disease. Here, we develop a deterministic system of differential equations to investigate the optimal vaccination coverage with a low-efficacy vaccine within the aforementioned parameter space. Despite simplifying assumptions, we illustrate that minimizing the overall infections does not necessarily correspond to the highest coverage of early vaccination. However, a high vaccination coverage, even with a low-efficacy vaccine, may still contribute to alleviating severe disease outcomes and reducing healthcare resource utilization.

[1] Wang, Z., Röst, G., Moghadas, S. M. (2019). Delay in booster schedule as a control parameter in vaccination dynamics. Journal of Mathematical Biology, 79(6-7), 2157-2182. https://doi.org/10.1007/s00285-019-01424-6

THE EXISTENCE OF BACKWARD BIFURCATION IN A MATHEMATICAL MODEL WITH THE CONCENTRATION OF VIRUS IN THE ENVIRONMENT: AN APPLICATION FOR COVID-19

Aytül Gökçe (Ordu University, Türkiye)
Other authors: B. Gürbüz, A. D. Rendall.

The COVID-19 epidemic has prompted a surge of research, with the definition, simulation, and rigorous mathematical analysis of epidemiological models. In this presentation, we delve into the scrutiny of a mathematical model designed to capture the spread of an infectious disease within a human population. This model incorporates factors such as imperfect vaccination and accounts for infections arising from virus particles present in the environment (fomites). To begin, we outline the central features of the model, a focal point of this presentation, and establish fundamental properties of its solutions. Of particular interest is the inclusion of a response function within the model, characterizing how the concentration of the virus in the environment influences the infection rate through this route. The response function is contingent upon an integer n¿0, and the primary role of this integer is pivotal in determining the existence of backward bifurcation within the system.

[1] Bulut, H., Gölgeli, M., Atay, F. M. (2021). Modelling personal cautiousness during the COVID-19 pandemic: a case study for Turkey and Italy. Nonlinear Dynamics, 105(1), 957-969. https://doi.org/10.1007/s11071-021-06320-7
[2] An sveir model for assessing potential impact of an imperfect anti-SARS vaccine. Mathematical Biosciences and Engineering, 3(3), 485-512.
https://doi.org/10.3934/mbe.2006.3.485

MATHEMATICAL MODELLING OF REPLICATION-MUTATION DYNAMICS OF CORONAVIRUSES

Konstantin Blyuss (University of Sussex, United Kingdom)
Other authors: Y.Kyrychko.

RNA viruses in general, and coronaviruses in particular, are fascinating in terms of living "on the edge": they have very fast replication rates associated with high mutation rates, thus forming the so-called quasi-species, i.e. swarms of closely related genetic mutants all related to and dominated by the viral master sequence. The advantage of this evolutionary strategy lies in creating a heterogeneous pool of phenotypes better able to adjust and respond to environmental change and selection pressure from their hosts. In most RNA viruses, high mutation rate is associated with RNA-dependent RNA polymerase (RdRp) that lacks proofreading capabilities and hence, cannot maintain fidelity during viral replication. In contrast, coronaviruses that have the largest genomes among all RNA viruses infecting humans, do have a special enzyme, exoribonuclease (ExoN) that is able to correct errors during viral replication. In this talk I will discuss a model of coronavirus replication with account for mutations and the effects of ExoN. I will consider different modes of viral replication, as well as the conditions for viral persistence and "error catastrophe", where mutations lead to viral extinction due to the loss of genetic information. We will also consider the effects of different classes of antiviral drugs acting through the inhibition of RdRp, an enzyme that is essential for replication of coronaviruses, inhibition of ExoN responsible for maintaining fidelity during viral replication, or through the mechanism of lethal mutagenesis.

PROBLEMS AND APPLICATIONS OF KINETIC MODELS FOR INTERACTING CELLULAR SYSTEMS

Ana Jacinta Soares (University of Minho, Portugal)

We present a cellular model with non-conservative interactions derived from the kinetic theory to study the immune system interactions. The model incorporates the ability of cells to reproduce a pattern of recurrence and remission dynamics. We then derive the corresponding macroscopic model describing the global behaviour of the interacting populations as the hydrodynamic limit of the kinetic model. The equilibrium solutions of the macroscopic model are determined and their stability properties are stated. Then we investigate the equilibrium states of the kinetic system and how are they related with the equilibrium states of the macroscopic model. We complete the study with some numerical simulations illustrating the analytical results.

[1] Della Marca, R. et al. (2022). Mathematical modelling of oscillating patterns for chronic autoimmune diseases. Mathematical Methods in the Applied Sciences, 45(11), 7144-7161. https://doi.org/10.1002/mma.8229

THRESHOLD DYNAMICS IN A PERIODIC TIME-DELAYED MODEL FOR MEASLES WITH PASSIVE IMMUNITY AND DOUBLE-DOSE VACCINATION

Attila Dénes (National Laboratory for Health Security, Bolyai Institute, University of Szeged, Hungary)
Other authors: M. A. Ibrahim, J. Mondal, P. Samui.

We establish and study a time-delayed model for measles transmission dynamics in a seasonal environment where delay stands for the average length of the latent period. In the model, we consider passive immunity of newborns obtained via transfer of maternal measles antibodies from mother to child, as well as double-dose vaccination. We define the basic reproduction number as the spectral radius of a linear operator and show that it serves as a threshold parameter for the global dynamics. We apply our model to real world data and present numerical simulations to assess the effectiveness of various control measures.

[1] Ibrahim, M. A., Dénes, A. (2023). Stability and Threshold Dynamics in a Seasonal Mathematical Model for Measles Outbreaks with Double-Dose Vaccination. Mathematics, 11(8), 1791. https://doi.org/10.3390/math11081791
[2] Opoku, S., Seidu, B., Akuka, P. N. A. (2023). A mathematical analysis of the impact of maternally derived immunity and double-dose vaccination on the spread and control of measles. Computational and Mathematical Biophysics, 11(1). https://doi.org/10.1515/cmb-2023-0106

EXPLORING DYNAMICS AND STABILITY IN A DENGUE FEVER TRANSMISSION MODEL WITH DELAY TERMS

Burcu Gürbüz (Johannes Gutenberg-University Mainz)
Other authors: A. Gökçe, S. I. Oke, M. O. Adeniyi, M. M. Ojo.

Dengue fever, a mosquito-borne disease caused by the dengue virus, poses a significant health threat, particularly in tropical regions. Characterized by a high fever and flu-like symptoms manifesting three to fourteen days post-infection, the disease necessitates a comprehensive understanding of its transmission dynamics for effective control measures. In this study, we delve into a model formulation of dengue fever transmission that incorporates crucial delay terms. Leveraging next-generation matrix techniques, we derive the basic reproduction number, a pivotal metric for assessing the potential spread of infectious diseases. Through a process of nondimensionalization, equilibrium points are obtained, laying the foundation for a detailed stability analysis of the delay model. Our investigation extends to numerical simulations, where specific parameters are considered, and the impact of time delays on disease dynamics is observed. By scrutinizing the stability of the model under delay, our research contributes valuable insights into the intricate dynamics of dengue fever transmission. This exploration not only enhances our understanding of the disease but also provides a basis for developing targeted strategies to mitigate its impact.

[1] Ojo, Mayowa M. et al. (2021). Modeling the dynamics of Lassa fever in Nigeria. Journal of the Egyptian Mathematical Society, 29(1). https://doi.org/10.1186/s42787-021-00124-9
[2] Li, X., Wei, J. (2005). On the zeros of a fourth degree exponential polynomial with applications to a neural network model with delays. Chaos, Solitons & Fractals, 26(2), 519-526. https://doi.org/10.1016/j.chaos.2005.01.019
[3] Gökçe, A. et al. (2023). Dynamics of a mathematical model of virus spreading incorporating the effect of a vaccine. arXiv. https://doi.org/10.48550/arXiv.2307.12707

RECENT DEVELOPMENTS ON TUMOR GROWTH MODELS: ANALYSIS AND SIMULATION

Xinran Ruan

Understanding the mechanisms of tumor growth is a timely and key challenge facing our society. Many partial differential equation models have been proposed to represent various aspects of tumor growth and therapy since the paper by H. P. Greenspan in 1972. In particular, in a plenary lecture at ICM 2014, B. Perthame reviewed two types of the model, one based on the fluid mechanical aspects and the other one based on the free boundary formulation. In the talk, B. Perthame marked the connection between the two types of the model by the so-called Hele-Shaw asymptotic. Such kinds of tumor growth models have simple forms and are easy to be generalized, and thus have attracted a lot of interest ever since then. A lot of new models have been proposed by generalizing the model to include new aspects or to describe new phenomena. This mini-symposium aims to provide a platform to present some newest developments of the tumor growth models. New aspects, such as necrotic cores and the heterogeneity inside a tumor, might be considered to construct new models. New numerical methods, which are stable and preserve the asymptotic relations, might be developed. By gathering junior and senior researchers working in the same area but from different backgrounds, we aim to spark new collaborations and offer a platform for scientific exchange.

PDE MODELS FOR THE SPATIAL SPREAD AND EVOLUTIONARY DYNAMICS OF HETEROGENEOUS CELL POPULATION

Tommaso Lorenzi (Politecnico di Torino)
Other authors: B. Perthame, X. Ruan, K.J. Painter, F.R. Macfarlane

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In this talk, PDE models for the spatial spread and evolutionary dynamics of heterogeneous cell populations will be considered. In these models, a continuous structuring variable captures intercellular variability in cell proliferation and migration rates. Analytical and numerical results summarising the behavior of the solutions to the model equations will be presented, and the insights generated by these results into the mechanisms that underpin collective cell migration will be briefly discussed.

[1] Lorenzi, T., Painter, K. J. (2021). Trade-offs between chemotaxis and proliferation shape the phenotypic structuring of invading waves. International Journal of Non-Linear Mechanics, 139, 103885. https://doi.org/10.1016/j.ijnonlinmec.2021.103885
[2] Macfarlane, F.R. et al. (2022). Individual-based and continuum models of phenotypically

heterogeneous growing cell populations. AIMS Bioengineering, 9(1): 68-92. https://doi.org/10.3934/bioeng.2022007

TUMOR GROWTH WITH A NECROTIC CORE AS AN OBSTACLE PROBLEM IN PRESSURE

Zhennan Zhou (Westlake University)
Other authors: Xu'an Dou, Chengfeng Shen

Motivated by the incompressible limit of a cell density model, we propose a free boundary tumor growth model where the pressure satisfies an obstacle problem on an evolving domain, and the coincidence set captures the emerging necrotic core. We contribute to the analytical characterization of the solution structure in the following two aspects. By deriving a semi-analytical solution and studying its dynamical behavior, we obtain quantitative transitional properties of the solution separating phases in the development of necrotic cores and establish its long time limit with the traveling wave solutions. Also, we prove the existence of traveling wave solutions incorporating non-zero outer densities outside the tumor bulk, provided that the size of the outer density is below a threshold.

[1] Dou, X. et al. (2023). Tumor growth with a necrotic core as an obstacle problem in pressure. arXiv. https://doi.org/10.48550/arXiv.2309.00065

MATHEMATICAL PROBLEMS IN A CLASS OF TUMOR GROWTH MODELS

Yu Feng (Peking University)
Other authors: L. Liu, Z. Zhou, M. Tang, X. Xu

In this talk, I will first introduce a class of tumor growth models described by porous medium equations (PME), which possesses a physical parameter m that characterizes the constitutive relation between cell density and pressure. And, one can obtain a Hele-Shaw type free boundary model by taking the incompressible limit (sending m to infinity). We then consider the forward and inverse problems in these tumor growth models. In the forward problem, we study the tumor boundary instability (the generation of finger-like structure) induced by nutrient consumption and supply based on the Hele-Shaw type model. While, in the inverse problem, we establish a Bayesian inversion framework for the PME models that perform uniformly well with respect to the constitutive relation parameter m.

[1] Feng, Y. et al. (2023). Tumor boundary instability induced by nutrient consumption and supply. Zeitschrift für angewandte Mathematik und Physik, 74(3).
https://doi.org/10.1007/s00033-023-02001-0
[2] Feng, Y., Lui, L., Zhou, Z. A unified Bayesian inversion approach for a class of tumor growth models with different pressure laws. arXiv. https://doi.org/10.48550/arXiv.2306.02060

STRUCTURE PRESERVING SCHEMES FOR TUMOR GROWTH MODELS

Xinran Ruan (Capital Normal University)
Other authors: N. David

Mechanical models of tumor growth based on a porous medium approach have been attracting a lot of interest both analytically and numerically. In this talk, I will show the stability properties, based on which we can further show the asymptotic preserving property, of some finite difference scheme for a model where the density evolves down pressure gradients and the growth rate depends on the pressure and possibly nutrients.

[1] David, N., Ruan, X. (2021). An asymptotic preserving scheme for a tumor growth model of porous medium type. ESAIM: Mathematical Modelling and Numerical Analysis, 56(1), 121-150. https://doi.org/10.1051/m2an/2021080

MATHEMATICAL MODELS FOR PEST DYNAMICS AND CONTROL

Sara Pasquali , Bedr'Eddine Ainseba

Pests are a great threat to humanity. They can cause severe damages to crops or human and animal health. In agriculture, pests are responsible for direct damage to plants and indirect damage because they can transmit infections to the crop. These damages cause loss of crops resulting in economic damage to farms. Other pests threaten human and animal health. For example, mosquitoes and ticks are among the most notorious vectors of disease transmission. Recently, the negative impacts of pests are increasing due to climate change and geographic expansion of their habitats. Public health authorities are involved in the identification and implementation of pest control strategies to mitigate their negative impact. Knowledge of pest dynamics under field conditions is a key factor for developing pest management strategies. Mathematical models are suitable tools to describe the dynamics of pests in time and space, and the ability to predict population dynamics under different environmental conditions can reduce the cost of control intervention. Population dynamics models are also at the basis of Decision Support Systems that aim to support control strategies.

The aim of this mini-symposium is to collect and present recent research on pest population dynamics useful for pest control. Topics include both applications to crop-dangerous pests and pests that threaten animal and human health. We bring together a group of 4 researchers with different backgrounds to highlight the interest in mathematical models for pests dynamics in various scientific areas. The speakers come from different countries and are at different career stages to give people an equal opportunity to present their research. The hope of the organizers is to create a network among participants engaged in this field to create possible future collaborations.

CONTROLLING BURROWING NEMATODES IN BANANA ROOTS BASED ON AN EPIDEMIOLOGICAL MODEL WITH VARIABLE INFESTATION DENSITY

Suzanne Touzeau (Université Côte d'Azur, INRAE, ISA, France; Université Côté d'Azur, Inria, INRAE, CNRS, MACBES, France)
Other authors: F. Kemayou, F. Grognard, S. Bowong

Bananas and plantains are a staple food crop in many countries in the tropics. Burrowing nematodes feed on banana roots, among other plants, and create major damages. As they spend most of their life cycle in the roots, their control is particularly challenging. To tackle this

issue, we developed a model describing the interactions between roots and nematode during a cropping season. This model considers a variable infestation density, a fairly original modelling feature in plant epidemiology. We analysed this model and studied its asymptotic properties. We showed that the model can exhibit a backward bifurcation, making it difficult to control the pest. We then introduced a control variable, which reduces nematode infestation. This type of control can be achieved by biostimulants, which activate plant defence mechanisms and hence have a nematode suppressive effect. We used optimal control theory to determine how best to apply this control. Using a crop yield proxy, our aim was to maximise the profit while minimising the final nematode population, to ensure minimal infestation and reasonable yield for the next cropping season.

PHYSIOLOGICALLY-BASED MODELS AND FIELD MEASUREMENTS: A GOOD BINOMIAL TO IMPROVE MODELS' PREDICTIVITY

Luca Rossini (Service d'Automatique et d'Analyse des Systèmes, Universitè libre de Bruxelles, Brussels, Belgium)
Other authors: N. Bono Rossello, M. Contarini, S. Speranza, E. Garone

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Physiologically-based models are pillars in the mathematical description of populations of insect pest and diseases since long time. The interest in these models is growing because of their implementation in Decision Support System (DSS) software, which can project the scenarios of the infestations in cultivated field for planning effective and sustainable control strategies. Despite the demand of DSS is increasing, the large-scale use of these tools is still limited. The reason behind this limitation is that to date models are mostly capable of describing the development of the populations a posteriori, with a constrained predictive range. An example at hand is the dependence of the equations on the initial conditions, that in the case of a population represent "the day zero" and the "initial abundance". From an applied point of view these parameters are almost impossible to estimate, given the high level of uncontrolled factors that characterize the natural environments. This precondition was the starting point of "PestFinder - Model-Based Estimation and Control of Agricultural Infestations Through Abiotic Changes" a two-year Marie Curie postdoctoral fellowship project funded by the European Commission, call HORIZON-MSCA-2022-PF. One of the activities of the project aims to formulate a theoretical framework that includes monitoring data as an active part of a pest population density model, overcoming the obstacle of estimating the initial conditions. As a first result, we propose the application of an estimator scheme in the form of an Extended Kalman Filter (EKF) to a revised physiologically-based model we introduced in previous studies. To test the method, we carried out a preliminary test by applying this theoretical framework to two species of agronomical relevance: Drosophila suzukii and Bactrocera oleae. These case studies show that the dependence of the simulation on the initial conditions and time zero is strongly reduced by using the EKF.

MATHEMATICAL MODELING OF PEST RESISTANCE TO INSECTICIDES AND GLOBAL DYNAMICS

Khadidja Aicha Kada (Department of mathematics, Faculty of Sciences, University of Tlemcen, Algeria)
Other authors: B. Ainseba, S.M. Bouguima

The European grapevine moth Lobesia botrana causes major economic damages in many European countries (France, Italy, etc.), North Africa, and in many Asian countries [1, 3]. As a massive use of insecticides, insects develops resistance. This is what ecologists call natural selection of the resistant individuals. But this can also happen when areas are treated with insecticides with little effect. In the first part of this presentation, we present a model without spatial structure describing the dynamics of insects including its resistance to insecticides. In the second part, we include in the model dispersal between different space patches. Individuals can move from one patch to another at a fast time scale with respect to the demographical time scale. Using this model, we aim to understand the main characteristics leading to persistence or extinction of the insect pest population.We establish global stability results. Numerical simulations provide some interesting insights on the dynamics of the pest population.

[1] Khadidja Aicha, K., Bedreddine, A., Sidi Mohammed, B. (2023). Mathematical modeling of pest resistance to insecticides in a heterogeneous environment. Mathematical Methods in the Applied Sciences, 46(12), 13320-13341. https://doi.org/10.1002/mma.9254
[2] Hemingway, J., Field, L., Vontas, J. (2002). An Overview of Insecticide Resistance. Science, 298(5591), 96-97. https://doi.org/10.1126/science.1078052
[3] Ainseba, B., Picart, D., Thiéry, D. (2011). An innovative multistage, physiologically structured, population model to understand the European grapevine moth dynamics. Journal of Mathematical Analysis and Applications, 382(1), 34-46.
https://doi.org/10.1016/j.jmaa.2011.04.021

CLIMATE-SENSITIVE DYNAMICALLY-STRUCTURED POPULATION MODELLING FOR THE CASTOR BEAN TICK, IXODES RICINUS

Iman Mehrabinezhad (Climate and Atmosphere Research Center (CARE-C), The Cyprus Institute, Nicosia, Cyprus)
Other authors: K. Erguler, L. Chitimia-Dobler, G. Dobler

Climate change, in combination with a number of socio-political factors, drives the expansion of habitable ranges of many vector species. As a consequence, the castor been tick, Ixodes ricinus, responsible for transmitting several animal and/or human pathogens, including tick-borne encephalitis virus and Borrelia burgdorferi (lyme disease), is expected to shift activity towards northern territories until the end of the century. Here, we developed a structured

population model to represent the dynamics of Ix. ricinus under the influence of climate and environmental drivers, such as temperature, humidity, land cover, and daylength. We employed the dynamically-structured matrix population model of Erguler et al. (2022) [1] to represent the complex life cycle behaviour, including various developmental stages, questing and feeding behaviour, and diapause. With this model, we present an improved understanding of the physiological dependence of the tick life cycle on climate and environmental variables. We quantify the overall tick activity under the seasonal variation of environment and derive essential indicators of public health relevance, including the relative fractions of questing and feeding stages and the beginning, end, and the modality of seasonal tick activity in high spatiotemporal resolution. The model will be integrated into the model repository of VEClim, https://veclim.com, an early warning support system for climate-sensitive vector-borne diseases, to predict habitat suitability and dynamic activity of Ix. ricinus and the risk of disease due to this vector. The platform will reliably inform public health professionals and policy makers and contribute to the global strategies of tick and tick-borne disease management.

[1] Erguler, Kamil et al. (2022). A dynamically structured matrix population model for insect life histories observed under variable environmental conditions. Scientific Reports, 12(1). https://doi.org/10.1038/s41598-022-15806-2

DECIPHERING INTRACELLULAR REACTION PROCESSES: BRIDGING STOCHASTIC MODELS WITH SINGLE-CELL MEASUREMENT TECHNOLOGIES

Elena Sofia D'Ambrosio

In the study of isogenetic cell populations, significant phenotypic variation is often noted, in large part attributable to the stochastic nature of gene expression. This randomness, crucial across biological scales, drives cellular 'noise,' impacting processes like cellular decision-making, cell cycle dynamics, and gene expression fluctuations. Advanced methodologies such as time-lapse microscopy, flow cytometry, and single-cell RNA sequencing have enabled detailed single-cell behaviour analysis. Yet, the complexity of intracellular reactions, compounded by stochastic gene expression and measurement noise, remains a challenge.

Incorporating stochasticity into mathematical models is vital for understanding cellular functions. Stochastic models, particularly for low molecular count scenarios, are insightful but are limited by high dimensionality and complex feedback in cellular networks. Chemical reactions in these models, occurring at various timescales, add to the complexity of analysis and computational modelling.

Innovative theoretical and computational approaches, including timescale separation, model reduction, and deep learning, have been developed to address these challenges. However, further advancements in computing and refinement of stochastic models are necessary, particularly for real-time single-cell imaging and matching experimental technology progress.

This mini-symposium aims to unite experts in chemical reaction networks, bridging systems biology and experimental technologies. It will discuss recent theoretical and computational method developments, their strengths and weaknesses. The goal is to foster new methods for analysing stochastic intracellular reactions and inferring biological mechanisms from single-cell data.

INFORMATION PROCESSING BY INTRACELLULAR SIGNALING NETWORKS

Andre Levchennko (Yale Systems Biology Institute, Yale University, USA)

Intracellular signaling networks are dedicated to processing and transmission of information about changes in the cellular micro-environment. Historically, they have been analyzed using biochemical and genetic approaches. Over the last decade, we and others have introduced the toolbox of the analysis that yields precise estimates of information transmitted in signaling events, measured in live cell populations, even if the corresponding signaling pathways are only

partially experimentally characterized. In this talk, I will summarize the key developments in this area over the last decade, and sketch the key current and future research directions.

SCALABLE INFERENCE REVEALS GLOBAL TRANSCRIPTION REGULATION FROM TIME-RESOLVED SINGLE-CELL TRANSCRIPTOMICS

Dimitris Volteras (Department of Mathematics, Faculty of Natural Sciences, Imperial College London)
Other authors: V. Shahrezaei, P. Thomas

The transcriptional activity of a gene can vary significantly from cell to cell and over time. Single-cell transcriptomics promises to exploit these variations to shed light at the mechanisms of transcriptional regulation. The classic protocols, however, only reveal a snapshot in time obscuring the absolute quantification of transcription rates and hindering model identification. It thus remains unknown what drives global transcription dynamics in single cells. We present a stochastic model of gene expression in growing and dividing cells that harnesses temporal dimensions of single-cell RNA-sequencing through metabolic labelling protocols and cell cycle reporters. We develop a parallel and highly scalable Approximate Bayesian Computation method that exploits dynamical correlations between labels to quantify absolute burst frequency, burst size and degradation rate on a transcriptome-wide scale. Using Bayesian model selection, we pinpoint genes with distinct transcription regulation and reveal that most genes scale transcription rates with cell size. We find that the cell cycle regulation of transcription occurs in waves of degradation followed by waves of burst frequency and size modulation. Our method makes it possible to remove technical noise of sequencing protocols and reveals true biological sources of transcriptional variation. Our findings thus highlight how transcriptional dynamics is orchestrated on a genome-wide level in single cells.

TRADE-OFFS BETWEEN COST AND INFORMATION IN CELLULAR PREDICTION

Pieter Rein ten Wolde (AMOLF)
Other authors: A. Tjalma, and V. Galstyan

Living cells can leverage correlations in environmental fluctuations to predict the future environment and mount a response ahead of time. To this end, cells need to encode the past signal into the output of the intracellular network from which the future input is predicted. Yet, storing information is costly while not all features of the past signal are equally informative on the future input signal. Here, we show for two classes of input signals that cellular networks can

reach the fundamental bound on the predictive information as set by the information extracted from the past signal: Push–pull networks can reach this information bound for Markovian signals, while networks that take a temporal derivative can reach the bound for predicting the future derivative of non-Markovian signals. However, the bits of past information that are most informative about the future signal are also prohibitively costly. As a result, the optimal system that maximizes the predictive information for a given resource cost is, in general, not at the information bound. Applying our theory to the chemotaxis network of Escherichia coli reveals that its adaptive kernel is optimal for predicting future concentration changes over a broad range of background concentrations, and that the system has been tailored to predicting these changes in shallow gradients.

REAL-TIME INFERENCE OF INTRACELLULAR DYNAMICS: A DEEP LEARNING APPROACH

Elena Sofia D'Ambrosio (ETH Zürich)
Other authors: Z. Fang, N. Rossi, A. Gupta, M. Khammash

In isogenetic cell populations, stochastic gene expression significantly influences phenotypic diversity, impacting cellular decision-making and gene expression stability. Technological advancements like time-lapse microscopy have advanced our understanding of single-cell dynamics, highlighting the complexity of intracellular processes. The interplay of stochastic gene expression and measurement noise adds complexity, posing challenges in accurately tracking and interpreting cellular behaviors.

To understand the complexities of genetic networks and intracellular reactions, tracking multiple biochemical species is essential. However, this is constrained by the limited number of available fluorescent reporters, thereby creating an inference problem of identifying hidden species from time-course measurements, such as those from time-lapse microscopy. This task, known as stochastic filtering, seeks real-time estimates of hidden species from partial observations, which is challenging due to the nonlinearity of chemical interactions and the high dimensionality of chemical networks [1].

To address this, motivated by the success of deep learning in solving high dimensional problems [2,3], we introduce a deep learning method tailored for solving the filtering problem, associated with continuous-time, noise-free observations. Utilizing auxiliary Markov processes, we define a martingale that yields filtering estimates at specific times. This martingale adheres to an almost sure relationship learned by a deep neural network. Trained with Monte Carlo simulations, the neural network predicts real-time behavior for new observation trajectories, eliminating the need for simulations for online estimates, unlike popular inference methods such as particle filters. This holds promise for real-time inference of hidden genetic circuit behavior from single-cell data time-course measurements.

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https://doi.org/10.1101/2022.10.18.512737
[2] Han, J., Jentzen, A., Weinan, E. (2018). Solving high-dimensional partial differential equations using deep learning. Proceedings of the National Academy of Sciences, 115(34), 8505-8510. https://doi.org/10.1073/pnas.1718942115
[3] Gupta, A., Schwab, C., Khammash, M. (2021). DeepCME: A deep learning framework for computing solution statistics of the chemical master equation. PLOS Computational Biology, 17(12), e1009623. https://doi.org/10.1371/journal.pcbi.1009623

FROM SINGLE CELLS TO MICROBIAL CONSORTIA AND BACK: STOCHASTIC CHEMICAL KINETICS COUPLED TO POPULATION DYNAMICS

Jakob Ruess (INRIA Saclay)
Other authors: C. Aditya, F. Bertaux, G. Batt, G. Ballif

At the single-cell level, biochemical processes are inherently stochastic. Such processes are typically studied using models based on stochastic chemical kinetics, governed by a chemical master equation (CME). The CME describes the time evolution of the probability distribution over system states and has been a tremendously helpful tool in shedding light on the functioning of cellular processes. However, single cells are not living in isolation but are part of a growing population or community. In such contexts, stochasticity at the single-cell scale leads to population heterogeneity and cells may be subject to population processes, such as selection, that drive the population distribution away from the probability distribution of the single-cell process.

Here, I will introduce a multi-scale modeling framework that allows one to capture coupled stochastic single-cell and population processes. I will show that the expected population distribution of such multi-scale models can be calculated by solving a modified version of the CME that is of the same dimensionality as the standard CME. I will then show how such models can be used to explain experimental data on plasmid copy number fluctuations and population growth in media that selects against cells that have lost the plasmid. Finally, I will present an optogenetic recombination system that allows one to partition yeast populations into different cell types via external application of blue light to cells and show how our modeling framework can be used to predict and control emerging dynamics of the population composition in response to time-varying light stimuli.

[1] Ruess, J., Ballif, G., Aditya, C. (2023). Stochastic chemical kinetics of cell fate decision systems: From single cells to populations and back. The Journal of Chemical Physics, 159(18). https://doi.org/10.1063/5.0160529
[2] Aditya, C. et al. (2022). Using single-cell models to predict the functionality of synthetic circuits at the population scale. Proceedings of the National Academy of Sciences, 119(11). https://doi.org/10.1073/pnas.2114438119
[3] Aditya, C. et al. (2021). A light tunable differentiation system for the creation and control

of consortia in yeast. Nature Communications, 12(1).
https://doi.org/10.1038/s41467-021-26129-7

HAWKES PROCESS MODELLING FOR CHEMICAL REACTION NETWORKS IN A RANDOM ENVIRONMENT

Mark Sinzger-D'Angelo (TU Darmstadt, Germany)
Other authors: H. Koeppl

Cellular processes occur in a heterogeneous context, rather than in isolation. We model such embedded processes as chemical reaction networks with stochastic reaction rates. By viewing the reactions as events, we establish a link between CRNs in a linear random environment and Hawkes processes. More precisely, the Hawkes process is obtained by a linearization of Snyder's filter for a Markov modulated counting process. We offer two applications. (i) In the experimental context, statistics of the environment that can be estimated robustly may be limited to the first and second-order statistics. Luckily, the approximating Hawkes process only depends on these. (ii) We propose this linearization as a reference model. Comparing it to the exact model, we may classify the qualitative behavior of trajectories as a linear or non-linear effect of the environment. We show case studies and analytical results on preserved first- and second-order statistics.

A SCALING ANALYSIS OF STOCHASTIC MODELS OF REGULATION OF PROTEIN PRODUCTION IN BACTERIAL CELLS

Philippe Robert (INRIA Paris)
Other authors: V. Fromion (INRAE), J. Zaherddine (INRAE and INRIA)

Motivated by a general principle governing regulation mechanisms in biological cells, we investigate a general interaction scheme between different populations of particles and specific particles, referred to as agents. Assuming that each particle follows a random path in the medium, when a particle and an agent meet, they may bind and form a pair which has some specific functional properties. Such a pair is also subject to random events and it splits after some random amount of time.

In a stochastic context, using a Markovian model for the vector of the number of paired particles, and by taking the total number of particles as a scaling parameter, we study the asymptotic behavior of the time evolution of the number of paired particles.Two scenarios are investigated: one with a large but fixed number of agents, and the other one, the dynamic case, when agents are created at a bounded rate and may die after some time when they are not paired.

A first order limit theorem is established for the time evolution of the system in both cases via the proof of an averaging principle. Limit theorems for fluctuations are also obtained.

UNBIASED ESTIMATION OF SECOND-ORDER PARAMETER SENSITIVITIES FOR STOCHASTIC REACTION NETWORKS

Quentin Badolle (ETH Zürich)
Other authors: A. Gupta, M. Khammash

Stochastic models for chemical reaction networks are increasingly popular in systems and synthetic biology. These models formulate the reaction dynamics as continuous-time Markov chains and for such models the estimation of parameter sensitivities is an important and challenging problem. Sensitivity values help in understanding the robustness properties of the network and guide the parameter inference process. In particular, second order sensitivities give curvature information about expected network outputs and are at the heart of numerically efficient optimization routines like Newton-type algorithms. Currently the only unbiased estimator for second order sensitivities is based on the Girsanov transformation and it often suffers from high estimator variance, particular when the sensitive parameters have small values. We develop a novel estimator for second order sensitivities by first deriving an integral representation of second order sensitivities and then demonstrate its efficiency through numerical examples.

GAUSSIAN PROCESSES AND INFERENCE FOR DYNAMICAL SYSTEMS

John Fricks

Developments in Functional Data Analysis and Machine Learning have brought new perspectives to estimation of parameters for Ordinary Differential Equations and other dynamics systems, which can define mechanistic models. Specifically, these new perspectives combining dynamical systems and Gaussian processes (broadly construed) allow for more complex modes of variation beyond the assumptions typically associated with least squares estimation. For example, Functional Data Analysis has introduced the concept of curve registration, where stochastic variation is present in the phase in addition to the amplitude of a curve. The Machine Learning perspective of Gaussian Processes allows us to use priors to impose regularity on the underlying solutions or proxies to the solutions, while still estimating parameters that may have particular scientific relevance, and this framework is particularly well-suited to handling partially-observed systems and inter-subject variability in a population context.

GAUSSIAN PROCESSES FOR THE INFERENCE OF PARTIALLY KNOWN MECHANISTIC MODELS USED FOR CLINICAL TRIAL DATA ANALYSIS

Julien Martinelli (Department of Computer Science Aalto University, Espoo)

Gaussian Processes (GPs) provide a natural way to encode prior beliefs over function spaces and can be seen as the probabilistic counterpart of the well-known kernel methods. As such, they are endowed with the universal approximation property and can aid in inferring partially known mechanistic models. Such models could describe the dynamics of antibody response, whose behavior is typically not fully understood when considering newly discovered viruses, e.g., the latest SARS-CoV-2 variants. The idea of combining a theory-driven component, like a mechanistic model relying on biologically grounded parameters, with a data-driven component, is better known as Grey-Box Modeling as presented by Takeishi and Kalousis. The aim is to leverage the generalization properties of the imperfect theory-driven part jointly with the flexibility inherent to data-driven models. While the latter is usually captured by a Deep Neural Network (DNN), this choice might not be suitable for health-related applications, where data measurements are often scarce and heterogeneous. Instead, the principled uncertainty quantification provided by GPs coupled with their ability to cope with the low-data regime makes them a suitable candidate for health-related applications.

In this talk, I will show how GPs can enhance partially known mechanistic models [1], effectively acting as a "model error" component that compensates for imperfect knowledge, while

providing diagnostics about the well-specified nature of the mechanistic model. I will focus on the case of heterogeneous data collected over multiple patients from a given population, which requires a specific treatment [2].

[1] Bhouri, M.A., Perdikaris, P. (2022). Gaussian processes meet NeuralODEs: a Bayesian framework for learning the dynamics of partially observed systems from scarce and noisy data. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences, 380(2229). https://doi.org/10.1098/rsta.2021.0201
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https://doi.org/10.1007/s10994-022-06172-1

CURVE REGISTRATION FOR MECHANISTIC MODELS: APPLICATION FOR TREATMENT EFFECT ANALYSIS

Quentin Clairon (Université de Bordeaux, Inria Bordeaux Sud-Ouest (équipe SISTM))

We tackle the curve registration problem in a semi-parametric context where we aim to learn time-warping functions from noisy observations of registered curves available for a whole population. Still, in our case a priori knowledge regarding the unregistered curve dynamics is available under the form of a parametric ordinary differential equations (ODEs). From this combination of descriptive non-parametric model and causal parametric one, we hope to locate as accurately and exhaustively as possible the effect of a treatment intervention. From the causal representation, we quantify treatment effects on well identified mechanisms, specified as ODE parameter covariates. From the descriptive one, we infer global action of treatment due to other mechanisms missed by the ODE but accounted for by time-warping functions, leading to distorted dynamics for treated subjects comparing to the control group. The interplay between the two models also allows us to quantify with descriptive devices global treatment effect on unobserved state variables linked to data through interactions specified by the ODE. In practice, the time-warping functions are approximated by Gaussian Processes finite basis decomposition such that their joint estimation with ODE parameters is cast as a non-linear regression problem solved by likelihood maximization in a mixed effect setting to account for inter-subject variability. We then analyze the effect of therapeutic vaccines on HIV positive subjects after the interruption of their antiretroviral therapy treatment. This is made from viral load temporal evolution measurement only and by using a time-warped version of a classic ODE model describing the interactions between target/infected cells and viruses. With the described procedure, we were able to quantify the effect of different vaccines on known mechanisms, such as viral infectivity, but also to enlighten a global, yet unexplained so far, effect on the dynamic of the unobserved infected cells.

MANIFOLD-CONSTRAINED GAUSSIAN PROCESSES FOR ESTIMATING AND ASSESSING DIFFERENTIAL EQUATION MODELS

Yuxuan Zhao (University of Waterloo)

We consider the estimation and assessment of differential equation models using time-course data from biology and chemistry experiments. In practice, experimental data are often noisy and sparse; moreover, some system components described by the model may not be observed. To address these challenges, we developed a method of Bayesian inference based on manifold-constrained Gaussian processes (MAGI), such that derivatives of the Gaussian process must satisfy the dynamics of the differential equations. MAGI completely bypasses the need for numerical integration and is thus fast to compute. First, we present the MAGI framework and show how it works for estimating the parameters and system trajectories for ordinary differential equations, including examples with unobserved system components. Second, we discuss our latest extension of MAGI to time-delay differential equations. Third, we illustrate how MAGI can be used to assess and select different models from experimental data.

PARAMETER ESTIMATION FOR ORDINARY DIFFERENTIAL EQUATIONS WITH TIME WARPING

John Fricks (Arizona State University)

Curve registration is a set of techniques to align functional data in the presence of time warping—phase variation in the functional observations. In this talk, we will present a Bayesian framework to estimate the parameters of an ODE model when the observations contain stochastic fluctuations in both amplitude and phase with a Gaussian process defining the time warping model. To facilitate such a framework, a new method for curve registration using Hamiltonian Monte Carlo will be presented along with a hierarchical model that links a basis fit of the data to solutions of an ODE model, allowing for parameter estimation.

COLLECTIVE BEHAVIOUR ACROSS SCALES: DRAWING PARALLELS FROM CELLS TO HUMANS

Andrei Sontag, Kit Yates

Understanding the principles governing self-organisation in multicellular systems and the collective decision-making in animal and human groups is crucial for unravelling the mysteries of complex biological and social phenomena. This mini symposium brings together four talks that explore the dynamics of collective behaviour, ranging from the self-organisation of multicellular patterns to the collective hunting of social spiders, the collective motion of locust groups and the collective decision-making of humans.

By delving into these seemingly multifaceted and disparate systems, our goal is to draw parallels between the underlying dynamics that govern them, untangling ubiquitous rules or mechanisms for collective decision-making. Each talk will feature fundamental mathematical tools for modelling and analysis, as well as underpinning experimental data. Together these combined theoretical/experimental approaches allow us to analyse biological systems in greater depth, to test hypothesis, and verify predictions.

This mini symposium unites researchers from three different countries, at various stages of their careers (1 PhD student, 2 postdocs, and 1 tenured academic) and from different backgrounds (mathematics, physics, and biology), to provide a broad perspective of collective behaviour and its interconnected nature.

SELF-ORGANIZATION IN MULTICELLULAR SYSTEMS: FROM COLLECTIVE MOTION TO STEM CELL PATTERNING

David Brückner (Institute of Science and Technology, Klosterneuburg, Austria)

Multicellular systems, such as tissues, organs, and whole embryos, are a spectacular example of self-organising non-equilibrium matter. These systems combine collective movement and biochemical signalling to establish intricate tissue shapes and patterns of different cell types. To ensure proper biological function, such patterns must be established reproducibly, by controlling and even harnessing intrinsic and extrinsic fluctuations. While the relevant molecular processes are increasingly well understood, a central theoretical challenge is to identify the basic physical principles of mechano-chemical communication in these complex systems, and to uncover how this communication controls patterning robustness. I will present an information-theoretic framework to mathematically define and interpret the reproducibility and robustness of self-organised patterns. This framework provides a normative approach for optimisation of cell signalling and mechanics, which predicts optimal operating regimes of self-organising systems.

Furthermore, I will show how this approach guides the development of mathematical models of mechano-chemical collective dynamics in multicellular stem cell assemblies, including artificial organ-like structures. This work opens up an avenue towards unifying the zoo of chemical and mechanical signaling processes encountered across different developmental systems by using a common information-theoretic language.

MECHANISMS UNDERLYING SYNCHRONIZATION DURING COLLECTIVE HUNTING IN SOCIAL SPIDERS.

Violette Chiara (Lund University (Sweden) and University of Cambridge (UK))

Inter-individual synchronization is a commonly observed phenomenon in a wide range of animal taxa and can be an important means of ensuring coordination. Synchronization of multiple agents requires communication, which can be disrupted by a noisy environment. Social spiders of the species A. eximius are famous for their impressive collective hunts, during which hundreds of individuals alternate short movements and stops in unison. The spiders use the vibrations produced by their prey and transmitted by the web to locate the prey. A particularity of this system is that moving spiders also create vibrations on the web, which induces a lot of noise. We combined field and modeling approaches to study the behavioral rules underlying this synchronization and discuss its biological significance. We showed that the trigger of a spider movement depends on the ratio between the vibrations perceived by the prey and the moving conspecifics. With this model, spider synchronization is extremely flexible and adapts rapidly to changes in the system. Overall, this model enables spiders to hunt effectively in a noisy environment, despite constrained communication.

COLLECTIVE DECISION MAKING IN LOCUST GROUPS

Kit Yates (University of Bath, UK)

Among the most striking aspects of the collective movement of many animal groups are their sudden coherent changes in direction. Recent observations of locusts have shown that this directional switching is an intrinsic property of their motion. Comprehending the factors that determine such switches is key to understanding the movement of these groups.

In recent experiments we were able to characterise the intrinsic switching dynamics of groups of between 5 to 100 locust nymphs in a homogeneous laboratory environment. At low densities motion appears disordered, while at high densities locusts march in a common direction, which may reverse during the experiment. Interestingly we have been able to reveal that locust groups appear to increase the randomness of their movements in response to a loss of alignment by the group.

Over a number of years we have developed a range of different individual-based models which also display density-dependent directional switching: from spatially extended self-propelled particle models to well-mixed individual-based model, in which demographic noise leads to the observed density-dependent effects.

Most recently we have specified a broad class of models in which neutral agents (representing non-moving locusts in our experiments) have a crucial role to play in consensus formation and change. These models can be parameterised to capture the locusts switching data accurately, but also have implications for other consensus decision making processes (e.g. voting).

In this talk I will review the experimental locust data and the earlier models that were used to represent them. I will then introduce our broadly applicable modelling framework incorporating neutral agents and explain how it not only captures the data more successfully, but also provides a more parsimonious and realistic explanation of true locust behaviour.

PATHWAYS FOR OVERTURNING CONSENSUS IN HUMAN COLLECTIVE DECISION-MAKING

Andrei Sontag (University of Bath, UK)

Political decisions are the epitome of how many aspects of our lives are determined by collective decision-making. However, active participation in collective decision-making is often highly variable, with many individuals temporarily abstaining from voting in the face of uncertainty. Whilst memory and noise have been found to aid consensus formation, the role of neutrality in collective decision-making is not well understood, and the level of individual behavioural complexity required for the emergence of group consensus is not well-characterised.

In this talk, I will show that symmetric autonomous systems with neutral intermediate states, such as voters of a two-party system who can abstain, present only two possible dynamical pathways for consensus switching. I will also show how experiments with human participants helped us verify our predictions. The typical pathway observed in our experimental data corresponds to an increase in the number of abstentions as the system transitions from one state of consensus to the other, suggesting that they play a critical role in facilitating consensus change by reducing the effective population size, making it more susceptible to fluctuations, as opposed to what has been previously believed.

Our findings provide a parsimonious explanation of consensus formation and change, giving insight into distributed decision-making protocols in animal and human collectives and suggesting efficient solutions to automated collective decision-making problems.

MULTISCALE MODELING & ANALYSIS IN NEUROSCIENCE

Zhennan Zhou

The complexity of the brain transcends traditional scales, encompassing intricate interactions from molecules to molecules, synapses to networks, and neurons to behavior. This mini-symposium delves into the powerful tools of multiscale modeling and analysis to illuminate the brain's symphony across levels. We gather presentations exploring the collective behavior of neuronal networks: Investigate network models capturing emergent phenomena like collective oscillations, synchrony, and information flow, bridging the gap between single-cell and population dynamics.

NOISE-DRIVEN BIFURCATIONS IN A NEURAL FIELD SYSTEM MODELLING NETWORKS OF GRID CELLS

Jose A. Carrillo (University of Oxford)
Other authors: A. Clini, H. Holden, P. Roux and S. Solem

In this talk I will review several results in the modelling of grid cells. The activity generated by an ensemble of neurons is affected by various noise sources. It is a well-recognised challenge to understand the effects of noise on the stability of such networks. We demonstrate that the patterns of activity generated by networks of grid cells emerge from the instability of homogeneous activity for small levels of noise. This is carried out by upscaling a noisy grid cell model to a system of partial differential equations in order to analyse the robustness of network activity patterns with respect to noise. This is rigorously achieved by mean-field type arguments. Inhomogeneous network patterns are numerically understood as branches bifurcating from unstable homogeneous states for small noise levels. We prove that there is a phase transition occurring as the level of noise decreases. Our numerical study also indicates the presence of hysteresis phenomena close to the precise critical noise value.

MODELLING OF GRID CELLS USING A NON-LINEAR AND NON-LOCAL FOKKER-PLANCK EQUATION

Pierre Roux (École Centrale de Lyon)
Other authors: J. A. Carrillo, S. Solem

Since their discovery in 2005 by Moser, Moser and colleagues, grid cells - specific neurons in the entorhinal cortex that play a crucial role in mammalian spatial navigation - have been the subject of numerous studies. A key point in their functioning is that they constitute modules whose electrical activity stabilises in a hexagonal pattern (which constitutes a kind of grid). In this talk, I will present a non-linear Fokker-Planck type partial differential model, developed by Carrillo, Clini, Holden and Solem, aimed at understanding the appearance of the hexagonal pattern and studying its robustness to noise. Through a mixture of theoretical results (local and global existence, convergence in relative entropy, noise-induced bifurcations) and numerical explorations, we have been working to improve our understanding of the model and of the underlying phenomenon.

A MEAN-FIELD LIMIT OF NEURAL NETWORKS WITH HETEROGENEOUS CONNECTIONS

Datong Zhou (Pennsylvania State University)
Other authors: P.-E. Jabin

We propose a generalized mean-field limit of biological neuron networks1. In contrast to established mean-field limits focused on networks with either identical connections or small perturbations around these homogeneous cases, our approach is applicable to completely heterogeneous network architectures. This paves the way for potentially deeper insights into a wider spectrum of neuron dynamics.

BLOW-UP TIME DILATION: CAPTURING THE SYNCHRONIZATION IN THE MEAN-FIELD PDE FOR INTEGRATE-AND-FIRE NEURONS

Xu'an Dou (Peking University)
Other authors: L. Tao, Z. Zhou

Networks of integrate-and-fire neurons have been described by a mean-field PDE at the population level, which is a nonlinear Fokker-Planck equation, known as the NNLIF model. An intriguing question is whether this population approach can capture events like synchronization

and multiple firing events for a finite number of neurons, as in those events the correlations between neurons are important. Mathematically, the synchronization has been connected to the blow-up of classical solutions for the mean-field PDE. This talk will present our recent attempts on this direction. We define physical generalized solutions for the mean-field PDE and develop numerical schemes for it. More specifically, we specify how to extend the classical solution beyond blow-ups, taking physical mechanisms such as the refectory periods into account. The idea is to dilate the blow-up time, resolving the blow-up by introducing a new, firing-rate-dependent timescale. Both the cases with or without intrinsic noise will be discussed. Numerical results will also be presented, including comparisons with the network of a finite number of neurons.

DIGITAL TWINS FOR CLINICAL ONCOLOGY AND CANCER RESEARCH

Guillermo Lorenzo, Chengyue Wu

The overall goal of this minisymposium is to present and discuss recent developments of digital twin technologies to (i) address the personalization and optimization of the clinical management of cancers, and (ii) advance the research of the biophysical mechanisms underlying these pathologies from the micro to the macroscale. A digital twin can be defined as a virtual representation of a physical object by means of a computational model (or a collection of models) that can continuously assimilate object-specific data to enable-decision making about the physical object based on its current and future states. Digital twins have undergone a widespread development in multiple areas of engineering (e.g., design, fabrication, and health monitoring of industrial products; energy and industrial plant operation; automatization of industrial components). Additionally, digital twins have been proven useful in several areas of medicine, such as surgical planning, cardiovascular disease interventions, convection-enhanced delivery of drugs to the brain, or glucose monitoring in diabetic patients. Given the increasing success of computational models to predict the development of cancer and its response to treatments, these models could be employed to construct digital twins to support the optimal diagnosis, monitoring, and treatment of individual patients as well as to assist the research of this disease in vitro, in vivo, and in silico. The talks in this minisymposium will present recent efforts in building digital twins for the clinical management of cancers and the (pre)clinical research of these diseases. The presentations will include a description of the specific area of application of the digital twins, the underlying models and computational techniques, the types of data required for their operation, performance metrics, and future developments.

PREDICTIVE MODELING IN RADIATION ONCOLOGY

Heiko Enderling (University of Texas MD Anderson Cancer Center)

The fields of cancer biology and clinical oncology are collecting a wealth of exciting data that both support and challenge our understanding of the biology underlying the responses seen in the clinic. Of utmost importance is the search for the optimal treatment combinations to eradicate targeted tumor and metastatic disease. Only few protocols have been modeled experimentally due to logistic limitations, and even fewer have been evaluated prospectively in the clinic. To exhaustively evaluate every possible treatment, alone or in combination in different orders and at all possible timings in vitro, in vivo and clinically is elusive. To fully decipher the complex cancer dynamics, a concerted effort is needed that integrates disciplines

that have not traditionally been consulted in experimental design and clinical studies. Mathematical modeling may provide the necessary tools to provide a mechanistic understanding of the many biological players and their interactions. The available preclinical data and outcomes from clinical studies are poised to help formulate, calibrate and validate purposely-built mechanistic mathematical models. Such models can then be used to simulate previously untested treatment protocols. Using machine learning and optimization theory concepts can then help identifying treatment approaches with the highest likelihood of success for subsequent experimental evaluation and validation. I will present a number of predictive models developed in our group towards the overall goal of predictive modeling for personalized radiation oncology.

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THERAPY OPTIMIZATION IN GLIOMAS: IN VIVO AND IN SILICO STUDY OF ALTERNATIVE DOSE SPACINGS

Juan Jiménez-Sánchez (University of Castilla-La Mancha)
Other authors: V.M. Pérez-García, J. Bosque, P. Sánchez-Gómez

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The Stupp protocol, a therapy scheme consisting of radiotherapy with concomi- tant and adjuvant chemotherapy, is the standard of care for glioblastoma, and is also used for high-risk low-grade gliomas. Although both tumour types develop in the brain, their characteristics – such as the percentage of proliferative cells or the presence of resistant cells – differ sufficiently to raise the question of whether the same treatment regime is the optimal choice for both.

In this work we explore whether extended dose spacings could improve the out- comes of standard therapy, with a focus on prolonging patient survival, delaying the onset of resistance and harnessing therapy-related toxicity. These unconventional spacings are based on the rationale that longer intervals between doses may allow persister cells, a transient reversible cellular state prior to the acquisition of full resistance, to revert to a sensitive state.

We integrate in vitro and in vivo experiments with discrete individual-based models to provide a simulation platform (validated with mice and human data) at the mesoscopic scale, that allows us to perform extensive virtual clinical trials, in search for alternative dose spacings that outperform the standard of care. The results gathered provide a valuable first step into the design of a real clinical trial, guided by in silico predictions.

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INTEGRATIVE KINETICS AND MACHINE LEARNING MODELING FOR PREDICTION OF OUTCOME FOLLOWING IMMUNOTHERAPY IN LUNG CANCER

Sébastien Benzekry (INRIA Sophia Antipolis Méditerranée)

I will present recent results from COMPO (COMPutational pharmacology and clinical Oncology) aiming at combining mechanistic modeling and machine learning ("mechanistic learning") to integrate longitudinal, multi-modal and high-dimensional data into predictive models of outcome following immunotherapy in non-small cell lung cancer (NSCLC). This will be based on two studies. The first leverages clinical trial data to help in drug development by predicting outcome of late-phase trials (e.g., phase 3) from early data (e.g., phase 2). The second is an integrative analysis of multi-modal deep-level biomarkers (multiplex immunohistochemistry, immune-monitoring, vasculo-monitoring, hematology and biochemistry) collected during the RHU PIONeeR. The results show substantial improvement of the predictive performances of classical markers (PDL1 expression, AUC = 0.64, tumor mutational burden, AUC = 0.65) using a novel kinetics-machine learning (kML) model (AUC = 0.86, c-index = 0.79, test set). The kML model was also able to predict the positive outcome of the phase 3 of the OAK trial (atezolizumab versus docetaxel) using 30 weeks on-study data (model HR = 0.802 (95% CI: 0.655 - 0.907)) while the observed data at this landmark time point was not conclusive (data HR = 1.04 (95% CI: 0.386 - 2.79)).

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DIGITAL TWINS IN LEUKEMIA TREATMENT

Ana Niño-López (University of Cádiz)
Other authors: S. Chulián, A. Martínez-Rubio, M. Rosa

At present, Acute Lymphoblastic Leukemia (ALL) accounts for 30% of cancers in pediatric patients. Despite the fact that survival has improved progressively in recent years, treatments are unsuccessful in 20% of that cases. For this reason, it is required to determine new therapeutic strategies to advance in this field and to develop computational models which describes leukemic cells behavior [1].

In this work, we mathematically analyse the induction phase in standard risk patients, based on SEHOP-PETHEMA-2013, current medical protocol in Spain, which associates each patient to their corresponding medication and dosage. We propose a mathematical model which computationally describes the behavior of leukemia in bone marrow from the studies about healthy bone marrow along with simulations about the leukemic clone evolution [2], on the basis of real data.

The results obtained in the study show how the risk of relapse is connected with the response in the first treatment phase [3]. We perform a new virtual patient classification depending on the minimal residual disease levels from blood cell samples from the patients on their eighth day of treatment.

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[2] Lorenzi, T., Marciniak-Czochra, A., Stiehl, T. (2019). A structured population model of clonal selection in acute leukemias with multiple maturation stages. Journal of Mathematical Biology, 79(5), 1587-1621. https://doi.org/10.1007/s00285-019-01404-w
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MATHEMATICAL MODELING OF MICROBIAL ECOLOGICAL SYSTEMS: BRIDGING THEORY AND EXPERIMENTS

Havva Yoldaş, Rebeca Gonzalez-Cabaleiro

This mini-symposium brings together leading researchers working at the intersection of mathematics, ecology and experimental biotechnology to explore recent advancements in the mathematical modeling of microbial ecological systems. Prominent examples of such systems appear in diverse environments from biofilm communities, waste water treatment systems, airborne microbial communities to human gut microbiota. When it comes to mathematical modelling, these complex and diverse systems share many common features. This minisymposium will focus on the presentation of advanced developments on mathematical models involving cross-diffusion or reaction-diffusion type partial differential equations, to deepen our understanding and capacity for quantification, of the dynamics that control the physiology and ecology of complex microbial communities. The session features presentations from mathematicians who have made significant contributions to the theoretical aspects of microbial ecological systems, but also applied scientists focusing on developing modelling to advance biotechnologies. Interdisciplinary discussions and collaborations will be fostered with the objective to advance predictive understanding and capacity for experimental validation. Topics to be covered include but are not limited to: recent mathematical developments in cross-diffusion and reaction-diffusion systems that appear on the modelling of microbial communities, spatial and temporal dynamics of biofilm formation in ecological contexts, incorporation of environmental factors and heterogeneity into mathematical models, validation and calibration of mathematical models using experimental data, and emerging trends and challenges in the mathematical modelling of microbial communities.

IMPACT OF AN OBLIGATE PREDATOR ON MICROBIAL ECOSYSTEMS: THE CHALLENGES AND BENEFITS OF COMBINING MODELLING AND HIGH THROUGHPUT CHEMOSTAT ARRAYS

J. Kimberley Summers (University of Warwick & University of Birmingham, United Kingdom)
Other authors: J.-U. Kreft

Mathematical modelling of biological species has a rich history of developing new theories of how species interact in both competitive and co-operative manners, including predatory and parasitic behaviours. Testing these theories with macro animal models is however challenging,

due to long generation times, relatively small numbers (where stochastic fluctuations can have large impacts) and hard to control environments. By contrast microbes make excellent model systems, generation times are in the order of minutes or hours, a single drop of liquid can contain millions, or billions of individuals and conditions can be highly controlled. Additionally, microbes are generally genetically tractable and have few or no ethical implications involved in their study. Most microbial studies of predation have involved either protist or viral predators, however both these predators are on different size scales to their bacterial prey. By contrast the obligate bacterial predator Bdellovibrio bacteriovorus while smaller than its prey is on a similar size scale and makes an excellent model to study the effects of predation. We present here a study on the effects of Bdellovibrio bacteriovorus on the population dynamics of small bacterial ecosystems (up to 2 prey and 1 decoy species) using a combination of mathematical modelling and an array of small scale chemostats. The results of the modelling were used to infer interesting conditions (substrate concentration and flow rate) for the experimental chemostats and the output from the chemostats highlighted areas where the model could be improved. We found it was possible to sustain all bacterial species within the chemostats for at least 1 month, but issues of contamination and especially biofilm formation frequently occurred. Our study highlights not only the potential benefits of combining modelling and experimental techniques, but also the challenges that need to be overcome to fully exploit this potential.

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DYNAMICS OF ENCAPSULATED BACTERIOPHAGE IN THE GASTROINTESTINAL TRACT

Carles Barril (Universitat Autònoma de Barcelona, Spain)
Other authors: S. Cuadrado, X. Bardina

Bacteriophage therapy consists in treating bacterial infections using viruses (bacteriophages) that kill bacteria selectively. Since bacteriophages degrade relatively fast in acidic environments, such as that found in the stomach of vertebrates, treatment of pathogenic enterobacteria can be enhanced by artificially encapsulating bacteriophages in microcapsules and, consequently, making them more resistant to natural degradation. Inside the microcapsules, however, bacteriophages are not able to infect bacteria so that efficient encapsulation requires microcapsules relatively permeable to the bacteriophages they carry. This permeability quality is somehow

antagonic to the protecting role microcapsules must also have, so that a trade-off does exist between them. In this talk we present a mathematical model to study this phenomena in different biological scenarios.

MATHEMATICAL MODELLING OF MICROBIAL ECOLOGICAL SYSTEMS: FUTURE DIRECTIONS

Havva Yoldas (Delft Institute of Applied Mathematics)
Other authors: M. Ribot, S. Labarthe, B. Laroche, P.-J. Hossie

This talk consists of a summary of the talks given during the mini-symposium, emphasising the open problems and possibility of future collaborations. If there is time, I will also briefly describe our ongoing collaboration with Rebeca Gonzalez Cabaleiro and Viktoria Freingruber (both from TU Delft) on the multiscale modelling of interacting microbial aggregates.

HETEROGENEOUS STRUCTURING IN TRAVELING WAVE SOLUTIONS OF A TRAIT-STRUCTURED KELLER-SEGEL MODEL

Viktoria Freingruber (University of Edinburgh & Heriot-Watt University, United Kingdom)
Other authors: T. Lorenzi, K. Painter, M. Ptashnyk

In this study we generalise the Keller-Segel (KS) model, a well-established framework used for investigating chemotaxis-driven invasion across diverse biological contexts. We extend the model to incorporate intrinsic heterogeneity within the cell population, represented by the percentage of occupied membrane receptors by ligands. This trait is subject to change through ligand attachment/detachment processes. The ligand serves a dual role as a chemoattractant and, in specific scenarios, a nutrient for cell proliferation. The resulting framework consists of a non-local partial differential equation governing the dynamics of the cell population, coupled with a diffusion reaction equation capturing the evolution of the ligand. Employing a Cole-Hopf transformation, we formally derive properties of traveling wave solutions, offering analytical insights into the system's behaviour. We conduct numerical simulations that align with our analytical results, thereby enhancing the applicability of the extended KS model. This work contributes valuable perspectives to the understanding of chemotaxis-driven invasion in heterogeneous cell populations and underscores the significance of trait-structures in modeling complex biological phenomena.

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UNRAVELLING THE DEBATE ON THE OXYGEN REQUIREMENTS OF COMAMMOX NITROSPIRA THROUGH THEORY-BASED MODELLING

Eloi Martinez-Rabert (University of Wisconsin-Madison, USA)
Other authors: C. J. Smith, W. T. Sloan, R. Gonzalez-Cabaleiro

Nitrification, the aerobic and two-step oxidation of ammonia to nitrate via nitrite, is a key process in natural and engineering systems. The last breakthrough in nitrification was the discovery of the complete ammonia oxidation by Nitrospira bacteria (also known as comammox Nitrospira). Comammox activity was firstly reported as dominant in extremely limited oxygen environments, where anaerobic ammonia oxidation was also occurring (anammox activity). This started a debate about the oxygen requirements for the chemoautotrophic growth of comammox Nitrospira. To explain comammox selection, an Individual-based Model was employed to simulate Nitrospira and anammox bacteria growth in suspended flocs assembled in a dynamic nitrogen and oxygen-limiting environment. The simulation results prove that even extremely low oxygen concentrations (¡1.5 μM) allow for a proportional growth of Nitrospira versus anammox bacteria similar to the one experimentally observed, but only when substance gradients throughout flocs and metabolic versatility of Nitrospira were considered. Additionally, a diversity of metabolic activities for Nitrospira was observed in all tested conditions, which in turn, allowed us to explain the observation of transient nitrite accumulation in environments with higher ammonia availability. This study shows how mathematical modelling can be used as a tool to direct experimentation by validating theoretical principles of microbial ecology, thus minimizing the complexity associated with the ecological systems and directing research exploration in a more efficient way.

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BIOENERGETIC METABOLIC MODELS FOR UNDERSTANDING AND DESIGNING OPEN MIXED CULTURE FERMENTATION PROCESS

Alberte Regueira (University of Santiago de Compostela, Spain)
Other authors: M. Mauricio-Iglesias, J. M. Lema

The production of volatile fatty acids in microbial open mixed culture fermentations has recently gained the attention of researcher and industry. While this is an attractive process to valorise waste streams, it also has its downsides. In particular, the characteristic poor and

variable product selectivity is a challenging problem for process design as the product spectrum is heavily influenced by environmental conditions without a systematic and mechanistic understanding or control. A possible avenue to tackle this issue via metabolic modelling, as this kind of models have the potential of gaining insight of the mechanisms governing mixed culture fermentations and offering prediction capacity for process design. In this talk, the development of novel bioenergetics model for mixed culture fermentations will be described for carbohydrates and proteins, the main constituents of waste streams. Additionally, the contributions of bioenergetics models to the understanding of microbial fermentations will be discussed as well as their capabilities to be used as early-stage process design tools.

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APPLIED MULTI-SCALE MODELLING METHODS IN DYNAMIC TISSUE REMODELLING

Arran B J Hodgkinson, Anna Zhigun

Multi-cellular organisms rely upon the large-scale reorganisation of tissue structures for healthy functioning, effected at the level of cell-scale biochemical reactions, whilst diseases are often caused by failures in the regulation of these processes. As such, tissue remodelling requires the coordinated movements of individual cells, resulting in population-scale tissue manipulations, constituting a challenging multi-scale paradigm for mathematical application, where novel methods are often key to breaking new ground.

This mini-symposium will present multiple methodologies for modelling biological problems where a complex interaction between cell- and tissue-scale give rise to phenomena with significance for the organism's biological function, as well as how data may be integrated into such modelling approaches to train, validate, and test real-world hypotheses. With applications focussing on cancer invasion and heterogeneity; tissue healing; and cellular reaction-diffusion processes, these models employ novel multi-scale techniques to increase flexibility and analytic depth.

A NUMERICAL STUDY OF POINT FORCES IN A MULTI-DIMENSIONAL ELASTIC MODEL FOR TUMORS

Fred Vermolen (Faculty of Sciences, Hasselt University, Belgium)

Tumors or cancer cells exert mechanical forces on their direct environment during their development and progression. A mathematical model can help to simulate the behaviour of forces for such types of cells and tissues in various ways. In this paper the impact of cellular forces on the surrounding tissue(s) (more specifically by cancer cells or by tumors) is considered. We consider the size of our cell (cancer/tumor) much smaller than that of the computational domain. Hence for this purpose, one simulates the forces by use of the Dirac Delta distributions. For this reason, momentum conservation is incorporated with the combination of linear elasticity equations and Dirac Delta distributions. The singularity issue caused by Dirac Delta Distributions for dimensionality greater than one, has been resolved by a singularity removing technique (immersed boundary method). A cell-based approach is formulated on the basis of the application of pulling (or pushing) point forces which are pointing inward (or outward) the cancer cell. The forces that are exerted by the cells are treated by the immersed boundary method. We study the model using the fundamental solution for linear elasticity which is obtained with the Green's function, where an integral representation is compared to approximate

finite summations. The proposed technique is numerically tested to confirm the validity of the approach. The results for the two-dimensional case show that upon increasing the number of point forces per unit peripheral length of the cell boundary, the displacement field converges to a limit. For three-dimensional case, we have observed the monotonically convergent behavior if we keep on refining the mesh over a spherical cell. We have quantified this convergence in terms of the L2-norm of the numerical solution. The paper also addresses well-posedness in terms of existence and uniqueness.

MULTISCALE MODELLING AND ANALYSIS FOR GLIOBLASTOMA MULTIFORME PROGRESSION AND RELAPSE

Dumitru Trucu (University of Dundee, UK)

Despite recent mathematical modelling advances, the understanding of the biologically multiscale process of tumour invasion remains an open question for all types of cancer. A notable challenge is presented by Glioblastoma Multiforme (GBM), the most aggressive primary brain tumour, which exhibits low survival rates due to its rapid growth, infiltration of surrounding brain tissue, and resistance to treatment. One major challenge is oedema infiltration, a fluid build-up that provides a path for cancer cells to invade other areas. MRI resolution is insufficient to detect these infiltrating cells, leading to relapses despite chemotherapy and radiotherapy. Building on our previous work [1-3], in this talk we present a new 3D multiscale moving boundary mathematical modelling for GBM invasion within fibrous heterogeneous environment focusing on exploring: (1) the GBM progression and oedema infiltrations; and (2) predict tumour relapses characteristics. To address tumour relapses, we explore several possible scenarios for the distribution of remaining GBM cells within the oedema after surgery. Furthermore, in this computational modelling exploration, all these tumour relapse scenarios are investigated assuming the presence of clinically relevant chemo-radio therapy. Numerical results suggest that a higher concentration of GBM cells near the surgical cavity edge led to limited spread and slower progression of tumour relapse. Finally, we explore mathematical and computational avenues for reconstructing relevant shapes for the initial distributions of GBM cells within the oedema from available MRI scans. The results obtained show good overlap between our simulation and the patient's MRI scan taken 850 days into the treatment. While still under analytical investigation, this milestone paves the way for robust reconstruction of tumour relapses from available clinical data.

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[2] Shuttleworth, R., Trucu, D. (2019). Multiscale Modelling of Fibres Dynamics and Cell Adhesion within Moving Boundary Cancer Invasion. Bulletin of Mathematical Biology, 81(7), 2176-2219. https://doi.org/10.1007/s11538-019-00598-w
[3] Trucu, Dumitru et al. (2013). A Multiscale Moving Boundary Model Arising in Cancer Invasion. Multiscale Modeling & Simulation, 11(1), 309-335. https://doi.org/10.1137/110839011

MATHEMATICAL MODELLING OF CANCER INVASION: PHENOTYPIC TRANSITIONING PROVIDES INSIGHT INTO MULTIFOCAL FOCI FORMATION

Zuzanna Szymańska (ICM, University of Warsaw)
Other authors: M. Lachowicz, N. Sfakianakis, M.A.J. Chaplain

The transition from the epithelial to mesenchymal phenotype and its reverse (from mesenchymal to epithelial) are crucial processes necessary for the progression and spread of cancer. We investigate how phenotypic switching at the cancer cell level impacts the behaviour at the tissue level, specifically on the emergence of isolated foci of the invading solid tumour mass leading to a multifocal tumour. To this end, we propose a new mathematical model of cancer invasion that includes the influence of cancer cell phenotype on the rate of invasion and metastasis. The implications of the model are explored through numerical simulations revealing that the plasticity of tumour cell phenotypes appears crucial for disease progression and local invasive spread. The computational simulations show the progression of the invasive spread of primary cancer reminiscent of in vivo multifocal breast carcinomas, where multiple, synchronous neoplastic foci are frequently observed and are associated with a poorer patient prognosis.

[1] Szymańska, Zuzanna et al. (2023). Mathematical modelling of cancer invasion: Phenotypic transitioning provides insight into multifocal foci formation. Journal of Computational Science, 75, 102175. https://doi.org/10.1016/j.jocs.2023.102175

HYBRID MODELLING OF SPATIALLY EXTENDED REACTION-DIFFUSION PROCESSES

Kit Yates (University of Bath)

Spatial reaction-diffusion models have been employed to describe many emergent phenomena in biological systems. The modelling technique for reaction-diffusion systems that has predominated due to its analytical tractability and ease of simulation has been the use of partial differential equations (PDEs). However, due to recent advances in computational power, the simulation, and therefore postulation, of computationally intensive individual-based models has become a popular way to investigate the effects of noise in reaction-diffusion systems.

Individual-based models provide accuracy but at the cost of significant computational resources. In a wide variety of biological situations, these computationally-intensive, high-resolution models are relevant only in particular regions of the spatial domain. In other regions, coarser representations may suffice to capture the important dynamics. Such conditions necessitate the development of hybrid models in which some areas of the domain are modelled using a coarse-grained representation and others using a more fine-grained approach.

In this talk I will discuss recent work from my group on connecting coarse and fine representations of reaction-diffusion phenomena. The models to be coupled will include both on and off-lattice individual-based representations of diffusion with and without volume exclusion as well as macroscopic partial differential equations. In each scenario we will demonstrate good agreement between our hybrid models and the full individual-based representation whilst achieving significant computational savings.

MODELLING COLLECTIVE CELL MIGRATION ACROSS SCALES: FROM INDIVIDUAL-BASED TO CONTINUUM MODELS

Juan Jiménez-Sánchez , Tommaso Lorenzi

Mathematical models have been increasingly employed to shed light on the spatiotemporal dynamics that underpin collective cell migration in a variety of biological processes. In particular, individual-based (IB) models, which track the dynamics of single cells, and their continuum counterparts formulated as partial differential equations (PDEs), which provide a population-level description of cell dynamics, have been used to investigate the mechanisms underlying tissue development, wound healing, and tumour growth. The aim of this mini-symposium is to bring together a group of researchers who have recently contributed to the development, study, and application of IB and PDE models of collective cell migration.

MACROSCOPIC LIMITS OF KINETIC EQUATIONS FOR INTERACTING MULTI-SPECIES SYSTEMS

Gissell Estrada-Rodriguez (Universitat Politecnica de Catalunya)
Other authors: T. Lorenzi

Experimental results on the immune response to cancer indicate that activation of T cells through interactions with cancer cells (D) can trigger a change in T cell migration patterns. In particular, while T cells in the pre-activation state (I) move in a non-local search pattern, the search pattern of activated T cells (A) is more localised. In this paper, we develop a kinetic model for such switch in migration modes. The model is formulated as a coupled system of balance equations for the one-particle distribution functions of populations I, A and D. T cell activation is modelled via binary interactions between a cell of population I and D. Moreover, cell motion is represented as a velocity-jump process, with the running time of I following a long-tailed distribution, which is consistent with a Levy walk, and the running time of population A following a Poisson distribution, which corresponds to Brownian motion. We formally show that the macroscopic limit of the model comprises a coupled system of balance equations for the cell densities whereby A movement is described via a classical diffusion term, whilst a fractional diffusion term describes the movement of I. The modelling approach presented here and its possible generalisations are expected to find applications in the study of the immune response to cancer and in other biological contexts in which switch from non-local to localised migration patterns occurs.

[1] Estrada-Rodriguez, G., Lorenzi, T. (2021). Macroscopic limit of a kinetic model describing the switch in T cell migration modes via binary interactions. European Journal of Applied Mathematics, 34(1), 1-27. https://doi.org/10.1017/S0956792521000358

MODELLING COLLECTIVE MIGRATION OF PHENOTYPICALLY HETEROGENEOUS CELL POPULATIONS: A MULTISCALE KINETIC APPROACH

Nadia Loy (Department of Mathematical Sciences "G. L. Lagrange", Politecnico di Torino)
Other authors: T. Lorenzi C. Villa

Cell migration plays a key organisational role in morphogenesis, it is essential to ensure successful wound healing, immune response and tissue homeostasis in adult organisms, and plays a crucial role in the progression of different pathological processes, such as in the metastatic cascade associated with cancer malignancy. Heterogeneity in the migration strategies adopted by cells is not only evident at the inter-population level, but has also been observed within the same cell population. In this talk I will, then, consider a phenotypically heterogeneous cell population, where cells may differ in structural properties which are implicated in cell migration. We focus on the case where the environment surrounding the cells can affect both reorientation processes that underly cell movement and mechanisms of phenotypic changes. I will then present a kinetic modeling framework for structured populations, allowing to start from a microscopic description by means of stochastic processes for both the migration strategy and the phenotypic changes. Then, a kinetic equation will be formally derived, allowing to depict the complete statistical mesoscopic description of the cell population taking into account both the velocity-jump process of cells and the phenotypic switches. In conclusion, macroscopic models for the cell density and average velocity will be derived in several regimes, according to the interplay of the two microscopic processes.

EVOLUTION OF PHENOTYPIC PLASTICITY LEADS TO TUMOR HETEROGENEITY WITH IMPLICATIONS FOR THERAPY

Simon Syga (Center for Interdisciplinary Digital Sciences (CIDS), Department Information Services and High Performance Computing (ZIH), TUD Dresden University of Technology, 01062 Dresden)
Other authors: H. Hatzikirou A. Deutsch

Cancer is a significant global health issue, with treatment challenges arising from intratumor heterogeneity. This study examines the complex relationship between somatic evolution

and phenotypic plasticity, explicitly focusing on the interplay between cell migration and proliferation [1]. We propose that evolution does not act directly on phenotypic traits, like the proliferation rate, but on the phenotypic plasticity in response to the microenvironment. We study this hypothesis using a novel, spatially explicit model that tracks individual cells' phenotypic and genetic states [2]. We assume cells change between mobile and growing states controlled by inherited and mutation-driven genotypes and the cells' microenvironment. We observe that cells at the tumor edge evolve to favor migration over proliferation and vice versa in the tumor bulk. However, this phenotypic heterogeneity can be realized by distinct regulations of the phenotypic switch, which depend on the apoptosis rate and the cells' ability to sense their environment. Emerging synthetic tumors display varying levels of heterogeneity, which we show are predictors of the cancer's recurrence time after treatment. Interestingly, higher phenotypic heterogeneity predicts poor treatment outcomes, unlike genetic heterogeneity.

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https://doi.org/10.1371/journal.pcbi.1009066

LINKING DISCRETE AND CONTINUOUS MODELS OF CELL BIRTH AND MIGRATION

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Self-organization of individuals within large collectives occurs throughout biology, with examples including locust swarming and cell formation of embryonic tissues. Mathematical models can help elucidate the individual-level mechanisms behind these dynamics, but analytical tractability often comes at the cost of biological intuition. Discrete models provide straightforward interpretations by tracking each individual yet can be computationally expensive. Alternatively, continuous models supply a large-scale perspective by representing the "effective" dynamics of infinite agents, but their results are often difficult to translate into experimentally relevant insights. We address this challenge by quantitatively linking spatio-temporal dynamics of discrete and continuous models in settings with biologically realistic, time-varying cell numbers. Motivated by zebrafish-skin pattern formation, we create a continuous framework describing the movement and proliferation of a single cell population by upscaling rules from a discrete model. We introduce and fit scaling parameters to account for discrepancies between these two frameworks in terms of cell numbers, considering movement and birth separately. Our resulting continuous models accurately depict ensemble average agent-based solutions when migration or proliferation act alone. Interestingly, the same parameters are not optimal when both

processes act simultaneously, highlighting a rich difference in how combining migration and proliferation affects discrete and continuous dynamics.

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THERMODYNAMICS OF LIVING SYSTEMS

Maarten Droste, Robert Planqué

This mini-symposium delves into the thermodynamics governing living systems. Life can be understood as an open out-of-equilibrium system, that exchanges energy and matter with its surroundings. Through conversions these can be exploited by the cell to maintain its internal processes, thereby growing, and preserving its structure and function. This interpretation allows one to use methods from thermodynamics and biophysics to describe and model living systems.

Understanding the thermodynamics of life is crucial in fields such as physiology, biochemistry and biotechnology. It provides insights into detailed metabolic processes but also allows for coarse-grained descriptions of complex biological systems. From the middle of the 20th century onwards, thermodynamic black-box descriptions such as energy converters have been used to study microorganisms without complete knowledge of their metabolism. Since the advance of genome scale models, resource-allocation models have been a useful tool to explain metabolic behavior in terms of limited resources distributed across internal processes.

In this mini-symposium, we bring together a geographically diverse group of experts at different stages of their academic career. They will show how they use and combine these theoretical approaches to understand properties of metabolic reactions and pathways in microbes, but also to explain behavior of entire organisms. The talks will consider thermodynamic aspects of specific metabolic processes such as polyhydroxyalkanoate synthesis in E. coli and cofactor specificities in metabolic networks. Furthermore, we will dive into the separation of metabolism in catabolic and anabolic processes and the role of thermodynamics in evolution. These modeling frameworks can provide tools to study design principles for metabolic engineering in microbes, which will also be discussed. Together, these talks will explore how properties of living systems follow from fundamental thermodynamic principles.

OPENING THE BLACK BOX: THERMODYNAMICS OF MICROBIAL GROWTH

Oliver Ebenhöh (Heinrich-Heine Universität Düsseldorf, Germany)
Other authors: N. Saadat, T. Nies

Microbial growth is often described as an energy converter, in which the catabolic breakdown of nutrients yields free energy which is partly used to drive the anabolic processes that assemble nutrients into new biomass. The combined effect of anabolism and catabolism can be described by a so-called "macrochemical" equation, which summarizes the chemical conversion of nutrients into catabolic waste products, biomass, and possibly other side products. Because such a

description of microbial growth completely ignores the details of intracellular metabolism, it is often termed a "black box" model of microbial metabolism. A diametrically different approach to describe metabolism is by genome-scale metabolic network models. Such models are derived from annotated genome sequences and ideally comprise all known biochemical reactions that can occur inside an organism.

We here investigate how these two concepts can be combined to study the thermodynamics of microbial metabolism. We illustrate how experimentally determined macrochemical equations can be systematically separated into a catabolic and an anabolic part. We then characterize these separate chemical equations by their thermodynamic properties and derive the generalized thermodynamic forces and flows that correspond to the affinities of catabolism and anabolism, and the corresponding catabolic and anabolic rates. With these data we challenge the common view that microbial energy conversion can be described by a linear energy converter model. Moreover, we employ genome-scale models to study how catabolism and anabolism are coupled through the production and consumption of ATP, and determine thermodynamic efficiencies. Finally, we observe a linear relation between the growth rate and the catabolic power, which appears to be species independent and may hint at a general principle in microbial growth.

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COMBINING THERMODYNAMIC, KINETIC AND PHYSIOLOGICAL TOOLS TO UNRAVEL BASIC AND APPLIED PROBLEMS IN MICROBIOLOGY

Karel Olavarria (Wageningen University, The Netherlands)
Other authors: M. C. van Loosdrecht, D. Machado de Sousa

Some bacteria can transform sugars and/or organic acids into polymers known as polyhydroxyalkanoates using different oxido-reduction processes. These processes share some similarities with the classic fermentations but the generated polyhydroxyalkanoates remain inside the cells. Although these processes have been documented at the physiological level for several decades, a more quantitative understanding of their rates (time) and extension (space) limits is a work in progress. Combining 13C-labeling, proteomics, controlled cultures in bioreactors, enzyme kinetics, stoichiometric modelling and thermodynamic approaches we have been exploring these processes in natural and engineered microorganisms. We have found evidence of a new glycolytic route operating in some of these organisms (basic outcome) and we have been working in a metabolic engineering strategy to produce more efficiently one of these polyhydroxyalkanoates (applied outcome). So far, our results show that a deeper understanding of the

physiological logic behind this oxido-reduction processes could make contributions to biotechnology, bio-remediation, synthetic biology, ecology and evolution. The aim of this presentation is to share our main findings, discuss the problems we are currently facing and hopefully find potential useful collaborators.

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[3] Guedes da Silva, L. et al. (2020). Revealing the Metabolic Flexibility of "Candidatus Accumulibacter phosphatis" through Redox Cofactor Analysis and Metabolic Network Modeling. Applied and Environmental Microbiology, 86(24).
https://doi.org/10.1128/AEM.00808-20

NETWORK-WIDE THERMODYNAMIC CONSTRAINTS SHAPE NAD(P)H COFACTOR SPECIFICITY OF METABOLIC REACTIONS

Steffen Klamt (Analysis and Redesign of Biological Networks, Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany)
Other authors: P. Stephanos Bekiaris

One characteristic and conserved property of the metabolism in all types of living cells is the co-occurrence of the two nicotinamide redox cofactors (or coenzymes) NAD(H) and NADP(H). This allows the cell to establish different redox potentials for the two coenzymes and thus to run simultaneously oxidation reactions (through low NADH/NAD+ ratio) and reduction reaction (by high NADPH/NADP+ ratio). However, it remains unclear what shapes the NAD(P)H specificity of each redox reaction.

We will present a computational framework to analyze the effect of redox cofactor swaps on the maximal thermodynamic potential of a metabolic network and use it to investigate key aspects of redox cofactor redundancy in Escherichia coli [1]. As one major result, our analysis suggests that evolved NAD(P)H specificities are largely shaped by metabolic network structure and associated thermodynamic constraints enabling thermodynamic driving forces that are close or even identical to the theoretical optimum and significantly higher compared to random specificities. Furthermore, while redundancy of NAD(P)H is clearly beneficial for thermodynamic driving forces, a third redox cofactor would require a low standard redox potential to be advantageous. With our method we can also predict qualitative trends of redox-cofactor concentration ratios and we show that the main results of our study are robust against assumed metabolite concentration ranges and thermodynamic parameters.

Overall, our framework provides a tool to study (or even design) optimal redox cofactor specificities in metabolic networks based on thermodynamic principles.

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THERMODYNAMIC MODELING FOR METABOLIC PATHWAYS

Elad Noor (Department of Plant and Environmental Sciences, Weizmann Institute of Science, Rehovot, Israel)
Other authors: W. Liebermeister

While evolution could choose between a vast space of possible metabolic pathways, only a tiny fraction of these variants is actually realized in nature, and a core part of central metabolism almost always follows the exact same design. The few exceptions that exist actually prove the rule, such as the two natural variants of glycolysis, or the small number of natural carbon fixation cycles. This cannot be explained just by historical contingency, as we see that evolution converged independently to the same solutions again and again, suggesting that there are criteria that make these pathways more "efficient" or "profitable" for a cell. We suggest that thermodynamic feasibility and the enzyme cost per unit flux are two important features by which pathways are selected and could serve as proxies for the cell's growth rate. Often, these criteria have a trade-off with the yield, creating a small set of Pareto-optimal choices. This might explain why we do find some level of pathway diversity in nature, as demonstrated by comparing the two versions of glycolysis. Beyond the study of natural processes, the design principles and analysis framework developed here have already had applications in several metabolic engineering projects.

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TRAVELLING WAVE PHENOMENA IN BIOLOGY

Lukas Eigentler, Mattia Sensi

Travelling wave phenomena are a hallmark of many processes in biology and ecology. Most commonly, they are associated with the formation of spatio-temporal patterns (e.g., dryland vegetation patterns, intertidal mussel beds) and invasion processes (e.g., cancer, non-native species). The vast number of systems underpinned by travelling waves, combined with the ubiquity of travelling wave phenomena in other fields, has led to the development of a large toolkit to better understand such dynamics. This minisymposium brings together recent advances on travelling wave phenomena in biology, primarily driven by early career researchers based in Europe, South America and the Middle East. Topics covered include spatio-temporal pattern formation of plants in drylands, collective migration phenomena driven by leader-follower dynamics, cellular migration during tumour growth, and theory on how travelling wave dynamics can prevent tipping in a range of ecosystems. The minisymposium also highlights the diversity of modelling and analysis tools available to shed more light on travelling waves; talks comprise results obtained through numerical simulations, numerical bifurcation analysis, numerical continuation, singular perturbation analysis, derivations of amplitude equations, multi-scale weakly nonlinear analysis, analyses of individual-based-models and more. Combined, the minisymposium provides insights into how mathematical modelling and analysis has provided us with an increased understanding of travelling waves across scales and systems. The relevance and ubiquity of periodic travelling waves in natural phenomena, and the variety of modelling and analytical approaches presented by the speakers hold the potential to induce significant, novel research leads and new collaborations.

HOW DIFFERENT FORMS OF LEADERSHIP IMPACT ON COLLECTIVE MIGRATION

Sara Bernardi (Politecnico di Torino)
Other authors: K. J. Painter

Efficient collective migration phenomena often rely on leader-follower group heterogeneity. In this respect, while the group partitioning into followers and leaders is conceptually straightforward, it remains a broad and indeterminate separation. Indeed, the leaders can be highly distinct from the rest of the group and, most likely, indifferent to whether the followers successfully complete their navigation. In other instances, leaders may be highly vested in the migration success of the followers and/or their guidance contribution may be more subtle, e.g. defined through a phenotypic trait which leads them to adopt a prominent role in the overall migration. In this talk, we explore the extent to which different "grades" of leadership impact

on collective migration processes. In particular, we extend the non-local hyperbolic framework of follower-leader dynamics formulated in [1] to investigate different types of leader behaviour. Analysis and numerical computation are used to characterize the various patterns displayed by the models, thus assessing the extent to which the migrating group is successfully steered towards the destination.

[1] Bernardi, S., Eftimie, R., Painter, K. J. (2021). Leadership Through Influence: What Mechanisms Allow Leaders to Steer a Swarm?. Bulletin of Mathematical Biology, 83(6). https://doi.org/10.1007/s11538-021-00901-8

SELF-ORGANISED PATTERNING IN CHEMOTAXIS OF MULTICELLULAR COMMUNITIES

Giulia Laura Celora (University College London)

Collective cell migration is ubiquitous amongst multicellular communities and contributes to many phenomena, e.g., morphogenesis and cancer metastasis. Yet, it is still not fully understood how cells coordinate to control the emergent collective motion of cell groups (or swarms). Recent experimental data reveal that physical interactions between cells within the swarms can result in emergent fluid-like properties and dynamics, such as periodic shedding, that can not be explained by conventional chemotaxis models, such as the Keller-Segel model. We propose an active fluid model to study how physical interactions affect the complex spatiotemporal dynamics of cell swarms' collective chemotaxis in response to self-generated chemical gradients. Numerical simulations reveal that the interplay between physical interactions, cell proliferation and chemotaxis is sufficient to explain the experimentally observed self-organised shedding of the swarm. In this talk, I will discuss how we can use numerical bifurcation analysis and travelling wave analysis to dissect model predictions and the role of physical interactions in mediating the swarm collective dynamics. I will conclude by highlighting how our work contributes to advancing the current understanding of self-organisation in chemotaxis of multicellular communities.

RETHINKING TIPPING POINTS IN SPATIAL ECOSYSTEMS

Swarnendu Banerjee (University of Amsterdam)
Other authors: M. Baudena, P. Carter, R. Bastiaansen, A. Doelman, M. Rietkerk

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The theory of alternative stable states and tipping points has garnered a lot of attention in the last decades. It predicts potential critical transitions from one ecosystem state to a completely different state under increasing environmental stress. However, typically ecosystem

models that predict tipping do not resolve space explicitly. As ecosystems are inherently spatial, it is important to understand the effects of incorporating spatial processes in models, and how those insights translate to the real world. Moreover, spatial ecosystem structures, such as vegetation patterns, are important in the prediction of ecosystem response in the face of environmental change. Models and observations from real savanna ecosystems and drylands have suggested that they may exhibit both tipping behavior as well as spatial pattern formation. Hence, in this talk, I will use mathematical models of humid savannas and drylands to illustrate several pattern formation phenomena that may arise when incorporating spatial dynamics in models that exhibit tipping without resolving space. I will argue that such mechanisms challenge the notion of large-scale critical transitions in response to global change and reveal a more resilient nature of spatial ecosystems.

THE ROLES OF FRONT INSTABILITIES IN REVERSING SPECIES INVASION AND DESERTIFICATION

Michel Ferre Diaz (Ben Gurion University of the Negev)

Invasion and desertification fronts represent two crucial ecological processes in ecosystem degradation that involve loss of biodiversity and ecosystem functioning and call for the study of ecosystem-recovery mechanisms. To this end, we study front instabilities in two reaction-diffusion models. Invasion is modeled by an extended Lokta-Volterra model for a native and an invasive plant species, where the presence of pathogens mediates the competition between them. For pathogens with an Allee effect, we identify a bistability range of counter-propagative fronts representing invasion and recovery dynamics. The two fronts differ in their pathogens levels at the narrow front zone. This result suggests ecosystem-recovery practices based on manipulating the pathogen level in the front zone. Desertification is studied using a model for dryland vegetation comprising equations for the vegetation biomass and the soil-water content. Earlier studies suggested that ecosystem recovery can be achieved through a transverse instability of a desertification front that grows vegetation fingers back into degraded areas. Based on the derivation of amplitude equations and a geometrical singular-perturbation approach, these studies provided insufficient information about the biotic and abiotic factors that control the instability threshold. Using a semi-analytical study, we uncover these factors and use our findings to delineate possible practices for reversing desertification.

TRAVELLING WAVES IN DRYLAND ECOLOGY

Gabriele Grifo (University of Messina)
Other authors: G. Consolo, G. Grifò, A. Iuorio, G. Valenti, F. Veerman

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In this talk, we will focus on the emergence of travelling waves in the context of dryland ecology. A large body of literature has shown how variation of environmental parameters may lead to catastrophic scenarios, such as desertification, and has contributed in identifying those ecological indicators of climate change and ecosystem resilience [1]. Among the mechanisms that are responsible for the emergence of such waves, the local biomass-water positive feedback constitutes the most relevant one. Unfortunately, it fails in ecosystems where water availability is not the limiting resource. This suggests that other ecological factors have to rule the evolution of travelling vegetation patterns, such as the presence of toxic compounds. The negative feedback associated to this latter contribution arises from the field observation that the same plant species cannot grow within the same region after a certain amount of time due to the increase in soilborne pathogens and an accumulation of autotoxic compounds [2]. With this in mind, in this talk we aim at emphasizing the role of toxic compounds in the dynamics of migrating vegetation patterns, forming along sloped terrains, as a function of the distance from the bifurcation threshold. To this aim, we consider an extension of the 1D Klausmeier model accounting for the presence of toxic compounds [3]. In detail, we first use linear stability tools to deduce the parameters' region in which patterns may arise and to capture the main features that characterize travelling band solutions at the bifurcating threshold. Then, we employ multiple-scale weakly nonlinear analysis to deduce the equation ruling the pattern amplitude evolution close-to-onset. Finally, we exploit geometric singular perturbation theory to study the qualitative behaviour of far-from-threshold pulse-type solutions. We also present several numerical results to corroborate analytical predictions and to extract additional ecological insights.

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https://doi.org/10.1016/j.physd.2023.134020

DERIVATION AND TRAVELLING WAVE ANALYSIS OF PHENOTYPE-STRUCTURED MODELS OF CANCER INVASION

Fiona Macfarlane (University of St Andrews)
Other authors: T. Lorenzi, K. J. Painter, X. Ruan

We have formulated models of cancer invasion wherein the infiltrating cancer cells can occupy a spectrum of states in phenotype space, ranging from 'fully mesenchymal' to 'fully epithelial'. The more mesenchymal cells are those that display more migratory phenotypes, where we examine both haptotaxis and pressure-taxis scenarios. However, as a trade-off, they

have lower proliferative capacity than the more epithelial cells. We have developed individual-based models that track the dynamics of single cells based on branching random walks over a lattice representing both physical and phenotype space. We have then formally derived the corresponding continuum model, which takes the form of partial integro-differential equations for the local cell population density function. Despite the intricacy of these model, for certain parameter regimes it is possible to carry out a detailed travelling wave analysis and obtain invading fronts with spatial structuring of phenotypes. As such, the model recapitulates similar observations into the structures of invading waves into leader-type and follower-type cells, witnessed in an increasing number of experimental studies over recent years.

NEGATIVE FEEDBACK DRIVING BIODIVERSITY: TRANSIENT BIOMASS DISTRIBUTIONS AND THE JANZEN-CONNELL HYPOTHESIS

Frits Veerman (University of Leiden)
Other authors: A. Iuorio, M. Baudena, M. Eppinga, F. Giannino, M. Rietkerk

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The emergence and maintenance of tree species diversity in tropical forests is commonly attributed to the Janzen–Connell (JC) hypothesis, which states that growth of seedlings is suppressed in the proximity of conspecific adult trees. As a result, a JC distribution due to a density-dependent negative feedback emerges in the form of a (transient) pattern where conspecific seedling density is highest at intermediate distances away from parent trees. Several studies suggest that the required density-dependent feedbacks behind this pattern could result from interactions between trees and soil-borne pathogens. However, negative plant–soil feedback may involve additional mechanisms, including the accumulation of autotoxic compounds generated through tree litter decomposition. An essential task therefore consists in constructing mathematical models incorporating both effects showing the ability to support the emergence of JC distributions. We develop and analyse a novel reaction–diffusion-ODE model, describing the interactions within tropical tree species across different life stages (seeds, seedlings, and adults) as driven by negative plant–soil feedback. In particular, we show that under strong negative plant–soil feedback travelling wave solutions exist, creating transient distributions of adult trees and seedlings that are in agreement with the Janzen–Connell hypothesis. Moreover, we show that these travelling wave solutions are pulled fronts and a robust feature as they occur over a broad parameter range; we calculate their linear spreading speed and show its (in)dependence on relevant nondimensional parameters.

TOPOLOGICAL DEFECT LAW FOR MIGRATING BANDED VEGETATION PATTERNS

David Pinto-Ramos (Universidad de Chile)
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Large-scale vegetation patterns, with wavelengths up to hundreds of meters, have inspired scientists to understand their origin and their influence on ecosystems. One global observation is that banded patterns generally appear on sloped territories, where the environment imposes a clear break of symmetry, favoring stripes with well-defined directions. Most models predict a perfect stripe pattern as the asymptotic state. Including the break of symmetry in mathematical models and realistic boundary conditions enables the formation of banded structures characterized by showing dislocations throughout the pattern. The pattern as a whole acquires a group velocity, propagating as a nonlinear wave with singularities, which is permanently sustained by boundaries. This same bifurcation from perfect bands to bands with dislocations is observed in three different models of vegetation biomass spatiotemporal evolution proposed in the literature. Surprisingly, this new dynamical regime could leave an imprint in the spatial distribution of dislocations, which is observed in actual vegetation banded patterns from Chile, Sudan, and North America, where we analyzed the distribution of dislocations together with the topography of the territory to unveil a clear break of symmetry, in line with our theory. We explore how ecologically relevant parameters could mediate the transition between the different dynamical regimes. Our work proposes that the break of symmetry due to the environment and the boundary conditions could play a crucial role in understanding these complex systems.

INFECTIOUS DISEASE OUTBREAK MODELLING ACROSS MULTIPLE SCALES

Shingo Iwami, Robin Thompson

Understanding phenomena in the life sciences requires consideration of processes occurring at more than one spatial scale. This is particularly true of infectious disease dynamics, with pathogen transmission arising at the cellular, individual, population (e.g. national) and multi-population (e.g. global) scales. There has therefore been increased interest in the development of epidemiological modelling approaches that incorporate dynamics at these different scales. In fact, assessments of both pharmaceutical and non-pharmaceutical interventions for limiting pathogen spread can be more accurate when multiscale models are employed rather than single scale models. For example, with a model that accounts explicitly for within-host pathogen dynamics, the impacts of antiviral treatment on viral load can be used to understand the relevance of antivirals for limiting population-scale transmission. Despite recent interest in multiscale infectious disease modelling, a range of challenges remain; including understanding when multiscale (rather than single scale) models are required and how to link data collected at different scales. In this mini-symposium, we will explore how epidemiological modelling has led to insights across multiple scales in a wide range of host-pathogen systems, and discuss future challenges in multiscale modelling. Crucially, the invited talks will facilitate discussions with a focus on solving real-world problems.

USING MODELS AT MULTIPLE SCALES TO ASSESS THE IMPACT OF SARS-COV-2 POTENTIAL VARIANTS OF CONCERN UNDER GRADUALLY RELAXING CONTROL MEASURES

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Viral reproduction of SARS-CoV-2 provides opportunities for the acquisition of advantageous mutations altering viral transmissibility, disease severity, and/or allowing escape from natural or vaccine-derived immunity. We use three mathematical models, with varying levels of multiscale detail: a parsimonious deterministic model with homogeneous mixing; an age-structured model, accounting for individual-level differences between hosts; and a stochastic importation model representing the importation of new infections to the region. We consider

variants of concern (VOCs) with different characteristics, including their transmissibility and immune escape from both natural and vaccine-derived immunity, and show how changing levels of control measures can affect the relative fitness of the various potential VOCs.

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MULTI-SCALE MODELLING OF MPOX ISOLATION STRATEGIES: THE IMPACT OF HETEROGENEITY IN INFECTIOUSNESS BETWEEN HOSTS

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Other authors: W. S. Hart, R. N. Thompson, F. Miura and S. Iwami

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Mpox is an infectious disease caused by the monkeypox virus (MPXV) which is part of the family of variola viruses. It causes smallpox-like symptoms including rash, lesions and fever. As of December 2023, there have been 92,976 confirmed cases and 172 deaths in the ongoing outbreak, primarily occurring in America and Europe. In response to the outbreak, isolation has been widely implemented as an essential nonpharmaceutical intervention (NPI). The US Centers for Disease Control and Prevention (CDC) have recommended an isolation rule for mpox patients involving isolation until all skin lesions have disappeared (i.e., a symptom-based rule) and suggested an isolation period of 2-4 weeks. However, due to considerable heterogeneity in the infectious period among mpox patients, this rule may lead to either a risk of ending isolation for those who are still infectious or an unnecessarily lengthy isolation period for those who are no longer infectious. Therefore, it is vital to assess the effectiveness of various isolation rules and to design an optimal strategy for ending isolation for mpox patients. In this study, we utilized a multiscale epidemiological model of mpox infection and evaluated three different isolation rules: the symptom-based (current approach), fixed-duration, and testing-based rules. We found that under the symptom-based rule, an additional period of 3 days compared to the current standard is needed to control the onwards transmission risk to an acceptable level. For fixed-duration and testing-based rules, the optimal isolation period was estimated to be 22 and 20.1 days on average, respectively. Additionally, under the same assumed level of acceptable risk, the testing-based rule effectively reduced the unnecessary isolation period more than the other two rules. These findings could be used to guide public health policy regarding rules for ending isolation of mpox patients.

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MODELLING DYNAMICS OF CITRUS DISEASE AT DIFFERENT SCALES

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Citrus production is threatened by citrus greening – aka huanglongbing – a bacterial disease of citrus that is vectored by psyllids. Impacts of huanglongbing on commercial citrus cultivation in the United States and Brazil have been particularly severe. Processes occurring at different scales not only affect transmission of diseases of humans, but also diseases of plants and animals. Driven by scales of available data, models of huanglongbing have often targeted small scale spread, via models tracking the disease status of individual plants (e.g., Cunniffe et al., 2015). These individual based models have been used to show how disease management based on removal of apparently uninfected plants can be successful, as well as to develop more sophisticated control methods based on the notion of epidemiological risk (Hyatt Twynam et al., 2017). Landscape scale models focusing on spread at much larger spatial scales have also been developed, tracking spread using a metapopulation of coupled stochastic compartmental models. These models do not purport to represent the disease status of every plant in the landscape, but instead track "host units", allowing for multiple host units per cell. This is a pragmatic compromise to allow for local disease dynamics without having to capture an unfeasible number of epidemiological transitions. A particular focus of landscape scale models has been surveillance, where they have been used to show how early detection can be optimized (Mastin et al., 2020). However, more recent work at landscape scales has focused on large-scale spread/control within the European Union. This is timely: the bacterium which causes huanglongbing is currently absent from the EU, although psyllid species capable of vectoring the pathogen have been detected in Spain, Portugal and Cyprus. We will describe insights from modelling studies at these different scales, and—as time permits—introduce work currently in progress which aims to understand in more detail

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MATHEMATICAL MODELLING OF EVOLUTIONARY CONDITIONS FOR VIRAL ONCOGENICITY

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Human oncogenic viruses were first identified in the 1960s, and subsequent research has implicated various viruses in the development of cancer. Most of these are DNA viruses, including Epstein-Barr virus, Kaposi's sarcoma-associated herpesvirus, and human papillomavirus. While these viruses produce evolutionary distinct viral proteins, they share similar oncogenic properties through targeting common tumour suppressor pathways, demonstrating convergent evolution [1]. One of these carcinogenic mechanisms involves disrupting the cell cycle regulation in infected cells, thereby promoting cell replication and potentially increasing total virus production. However, this replication advantage is balanced by the disadvantages of increased immune exposure and the associated risk of immune clearance, highlighting an evolutionary trade-off between viral replication and immune surveillance. Although previous studies [2 3] have explored oncogenic viral dynamics within and between hosts in the context of virulence evolution, the evolutionary conditions that have led to the current oncogenic properties of viruses still need to be better understood. To elucidate the evolutionary conditions under which viruses acquire oncogenicity, we have developed a novel mathematical model based on previous research [2, 3] that captures the interactions between the virus and the immune system. Our results suggest an optimal transformation rate at which infected cells acquire oncogenic properties to maximise viral fitness, depending on the differences in immunogenicity and immune-mediated elimination between infected and pre-cancerous cells. In this presentation, we will discuss our findings and propose principles governing the evolution of oncogenic viruses.

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POSTERS

MINIMUM COMPLEXITY DRIVES REGULATORY LOGIC IN BOOLEAN MODELS OF LIVING SYSTEMS

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The properties of random Boolean networks have been investigated extensively as models of regulation in biological systems. However, the Boolean functions (BFs) specifying the associated logical update rules should not be expected to be random. In this work, we explore various biologically meaningful types of BFs and provide a systematic study of their preponderance in a compilation of 2,687 regulatory rules extracted from published Boolean models reconstructed in a wide range of species and spanning diverse range of biological processes. A surprising feature is that most of these BFs have odd 'bias', that is, they produce 'on' outputs for an odd number of input combinations. Upon further analysis, we explain this observation, along with the enrichment of read-once functions (RoFs) and its nested canalyzing functions (NCFs) subset, in terms of two complexity measures: Boolean complexity [1] based on string lengths in formal logic, which is yet unexplored in biological contexts, and the so-called average sensitivity [2]. RoFs minimize Boolean complexity and the NCFs minimize not only the Boolean complexity, but also the average sensitivity for any given number of inputs and odd bias. These results reveal the importance of minimum complexity in the regulatory logic of biological networks.

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INTEGRATIVE KNOWLEDGE- AND DATA-DRIVEN QSP MODELING OF NEURODEGENERATIVE DISEASES: A CASE STUDY TARGETING ALS

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Complex diseases benefit from a personalized approach to treatment and prevention, which can be informed by mechanistic modelling and machine learning (ML) techniques. In neurodegenerative diseases such as spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS), serum neurofilament (Nf) is gaining relevance as a biomarker to assess axonal damage and monitor disease progression. A Quantitative Systems Pharmacology (QSP) model of Nf trafficking in healthy adults and SMA patients has been developed by Paris et al., providing a platform for predicting time-dependent serum Nf in various conditions. By incorporating this model into a mechanistic understanding of widespread neurodegenerative diseases, we can establish a framework to leverage interindividual variability in disease phenotypes and clinical data, moving towards a precision medicine approach. The present work aims to develop a multi-layer mechanistic model targeting ALS as a case study, which will extend the existing Nf platform. Relevant biological pathways will be extracted via literature mining. In addition, variables of interest and drivers of disease will also be identified by analysing the clinical data of ALS patients using statistical analysis and ML techniques. The extracted knowledge will be formalized as a network of molecular and cellular processes translated into a mathematical description as a system of Ordinary Differential Equations. The model's parameters will finally be estimated using model fitting techniques informed by literature research. To facilitate adoption in clinical practice, our model's structure will consider the accessibility of the measurements needed for parameter calibration. This research could provide a hypothesis-testing computational framework to assist drug development and clinical trials. Moreover, it could pave the way for the application of personalized treatments in clinical practice, improving the prognosis and well-being of ALS patients.

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MATHEMATICAL MODEL OF ADIPOCYTES SIZE DISTRIBUTION : COMPUTATION AND STUDY OF EQUILIBRIA

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Obesity is nowadays a global public health issue [1]. It is defined as an excess of lipids stored that harms health. The adipose tissue is in charge of this storage via its main cells : adipocytes. These cells present a singular property: their size varies from 10μm up to 150μm of diameter and the distribution is bimodal, presenting 2 characteristic sizes (around 30μm and 130μm with an inter-individual variability). Identifying the underlying mechanisms of this bimodality as well as the consequences on the dynamics of adipose tissue is a crucial issue to apprehend obesity.

In this work we reproduce adipocyte size distributions to better understand the origin of its particular shape. The model we consider proposes a simple mathematical explanation of the adipose tissue size distribution bimodality [1], assuming the size of adipocytes only depends on the amount of lipids stored in. We consider a system of Ordinary Differential Equations (ODE) that aims at describing adipocyte size taking into account lipid fluxes. In this system each equation describes a cell lipid content evolution over time. The extracellular lipid amount over time is also described, and constitutes the coupling term. However, the variability within the cell population is not described in the initial model. So the modeled size distributions are not realistic (they are made of one or two Dirac distributions).

Making the assumption that size distributions result from a system at equilibrium, we study the steady state of the ODE system previously described. By simulation, we assessed the hypothesis of intrinsic variability of cells, varying within the population a few key parameters. We show that it allows us to qualitatively reproduce the size distribution measured in rats or human adipose tissue. Also, we demonstrate the plausibility of a mono-stable profile for the majority of cells. These results will be discussed and perspectives including adipogenesis will be presented.

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MEAN-FIELD MODELS OF NEURAL POPULATIONS: INFLUENCE OF ADAPTIVE SYNAPTIC COUPLING

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Currently, the study of neural populations is of increasing interest. Two mean-field models of populations of coupled neurons allow to study the macroscopic quantities of a network of quadratic integrate-and-fire neurons with adaptive synaptic dependence in [1] and without it in [2]. In this presentation we show how these models are linked through a parameter related with the synapsis [3] and how the dynamics evolves when this parameter changes. We detect three main dynamical regimes in these coupled mean-field models (Rössler-type, bursting-type, and spiking-like dynamics), which opens the question of which regime is the most suitable for realistic simulations of large neural networks and shows the appearance of chaos when the synaptic adaptation is very weak. Finally, the macroscopic and microscopic dynamics are analysed.

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MODEL ORDER REDUCTION TECHNIQUES FOR PATTERN FORMATION IN A CHEMOTAXIS MODEL

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Other authors: F. Diele, D. Lacitignola, C. Marangi

In this talk we are interested in a suitable application of Model Order Reduction (MOR) techniques for the numerical approximation of spatial patterns, that are stationary solutions of reaction-diffusion-chemotaxis PDE systems. First of all, we will consider the well-known Keller-Segel model [1] with a logistic growth term [2] that admits stationary spatial patterns as solutions. Then, we will con- sider a variation of the Keller-Segel model, with the reaction part modified to fit the MOMOS model with density-dependent microbial turnover [3]. We will show that MOR techniques are able to reproduce the spatial patterns arising form Keller-Segel and MOMOS model. Acknowledgements. Funder: Project funded under the National Recovery and Resilience Plan (NRRP), Mission 4 Component 2 Investment 1.4 - Call for tender No. 3138 of 16 December 2021, rectified by Decree n.3175 of 18 December 2021 of Italian Ministry of University and Research funded by the European Union – NextGenerationEU; Award Number: Project code CN 00000033, Concession Decree No. 1034 of 17 June 2022 adopted by the Italian Ministry of University and Research, CUP B83C22002930006, Project title "National Biodiversity Future Center - NBFC".

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EFFICIENT RADIAL-SHELL MODEL FOR 3D TUMOR SPHEROID DYNAMICS WITH RADIOTHERAPY

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Other authors: F. Franke, S. Michlíková, S. Aland, L. A. Kunz-Schughart, S. Lange

Approximately 50% of patients diagnosed with cancer receive radiotherapy at least once during their disease. Experiments with sophisticated in-cellulo assays to improve radiotherapeutic outcomes are challenging, and some critical details of tumor cell dynamics still need to be explored. To enhance the informative value of such approaches and to support future therapeutic study designs, we develop an efficient mathematical model for three-dimensional multicellular tumor spheroids, which reflect microregions within a large tumor or avascular micrometastases and which are an auspicious experimental framework to pre-assess the curative effect of radio(chemo)therapy. We validate our mathematical model using experimental tumor spheroid growth data of several cell lines with and without radiotherapy and observe equal or better performance than previous models. Moreover, our model facilitates an efficient parameter calibration within previously reported and physiologically reasonable ranges and allows to explain the characteristic dynamics at small tumor volumes.

INFORMATION TRANSMISSION THROUGH STATE PERTURBATIONS IN METABOLIC NETWORKS

Arthur Lequertier (INRAE, MaIAGE)
Other authors: W.Liebermeister

Bacterial metabolism can be mathematically represented as a large network of chemical reactions. In such networks, propagating perturbations can carry information about environmental perturbations. To quantify this information, we need to study the responses of bacterial components in the presence of noise. Here, we study the system response to perturbations following probability distributions. Mutual information between model variables is used to quantify their dependencies as a form of information transfer. We expect that work will help us understand the signal-processing capacities of bacteria, taking into account internal and environmental noise and uncertainties.

CELL GEOMETRY EFFECTS ON ANTERIOR-POSTERIOR POLARITY FORMATION USING GROWING DOMAIN MODELS

Asayuki Kitajima (Faculty of Science at Kyoto University and Institute for the Advanced Study of Human Biology (ASHBi) at Kyoto University Institute for the Advanced Study (KUIAS))

Other authors: S. Seirin-Lee.

Anterior-Posterior (AP) polarity formation of cell membrane proteins is an essential process for asymmetric cell division, which is a critical mechanism to give rise to cell diversity in early development process. C. elegans embryo is a well-studied biological model to understand the polarity formation in both experimental and mathematical approaches. In the fertilized egg cell, anterior PAR proteins (aPAR) and posterior PAR proteins (pPAR), which are homogeneously distributed in the membrane and cytosol respectively in an initial stage, generate mutually exclusive polarity domains in cell membrane induced by mutual inhibition between aPAR and pPAR based on a membrane-cytoplasmic translocation dynamics. Mathematically, aPAR-pPAR polarity mechanism also has been well-studied and a mass conservation reaction-diffusion system was postulated as a key structure to make a polarity pattern in many previous studies . On the other hand, the effect of cell geometry on polarity formation has not been fully investigated, although it has been found that cell shape may play a crucial role in regulating a polarity formation . Therefore, in this study, to gain a comprehensive understanding of the cell geometry effect on polarity formation, we developed two generalized mathematical models by which we can explore the effects of both cell size and geometry on polarity pattern formation. To introduce these two models, we applied an idea of growing domain on reaction-diffusion system . Our results show that cell size and shape can be auxiliary key players to improve the robustness of polarity patterning and can affect polarity formation differently depending on the three phases of polarity formation: symmetry breaking, emergence, and maintenance phases.

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INFERRING THE DYNAMICS UNDERLYING PROTRUSION-DRIVEN CELL MOTILITY

Avinash kumar Basavanaga (University of Potsdam)
Other authors: Cristina Martinez T, Matthias Holschneider, and Carsten Beta

Amoeboid cell motility is a crawling-like cell migration that plays an important role in multiple biological processes such as wound healing, morphogenesis, and cancer metastasis. It is characterized by deformations of the cell membrane that are orchestrated by coordinated actions of the actin cytoskeleton and controlled by an intracellular signaling network. Mathematical modeling offers a powerful tool to decode the complex patterns of cell shape associated with the expansion and contraction of the cell membrane.

In the past, many computational models have been proposed to describe the locomotion of amoeboid cells, with the most widely used model based on a dynamic phase field driven by an intracellular reaction-diffusion system. We are working with a three-component contour dynamical model, where the components are curvature, area preservation, and the concentration of actin in the cell. In this model, the concentration of actin is carried between two consecutive steps. With the help of Kalman filtering, we add a memory property to the actin concentration, allowing us to quantify the cell evolution.

Our goal is to establish a systematic, data-based framework for the comparison and improvement of this class of motility models. Based on previously developed cell contour analysis to quantify cell shape dynamics and a well-established three-component contour dynamical model to simulate and analyze cell motility in two dimensions, we will focus on a systematic comparison of this model to experimental data, along with establishing related data assimilation techniques.

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GRAPH HOMOGENEITY ANALYSIS OF SINGLE-CELL EPIGENETIC STATES

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The prevailing interpretation of Waddington's landscape is that attractors in gene expression space produce and stabilize distinct cell types. This hypothesis motivates the standard practice of clustering cells in single-cell omics data, prior to the analysis of differential gene expression. Yet in practice, the analysis of single-cell data has revealed incredible heterogeneity in cell state, regardless of the particular measurement technology employed. Indeed, in our previous work we observe ubiquitous, fractal-like density distributions of single cells in epigenetic space, that are inconsistent with the expected densities that would be produced near a cell-type attractor. This extreme heterogeneity of single-cell data poses a challenge for the robust identification of cell types in epigenetic space. For example, when the standard analytical pipeline applies nonlinear transformations and dimensionality reduction steps to fractally distributed data, the produced cell-type clusters are often very parameter sensitive and difficult to reproduce. In this work, we propose an alternative method for asking questions of single-cell data that is directly informed by the underlying structure of the data. We develop a graph-homogeneity approach to more finely characterize how tissue composition changes in health and disease. Without clustering the data, we characterize differences in gene expression across local regions of interest, and report reproducible findings across experimental replicates.

DEEP LEARNING CHAOTIC ANALYSIS OF BIOLOGICAL TIME SERIES: FROG HEART DYNAMICS

Carmen Mayora-Cebollero (University of Zaragoza)
Other authors: R. Barrio, F. H. Fenton, M. J. Toye

Classical techniques as Lyapunov Exponents are usually used to study the behaviour of dynamical systems. Real data has some drawbacks as short and noise recordings, which can cause imprecise results when performing chaotic analysis with such classical tools. Moreover, when dealing with large datasets, it is necessary to have an automatic algorithm for the analysis as human intervention on the whole dataset is not feasible. Recently, some authors have used Deep Learning to detect chaos in a dynamical system [1, 2, 3]. In this presentation, we propose to apply a Deep Learning algorithm to perform a chaotic analysis in biological time series of a frog heart.

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TRANSCRIPTOME-STRUCTURED POPULATION MODELS FOR NEURAL STEM CELLS

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Adult neurogenesis represents the generation of neurons from neural stem cells, which have been known to be in two states: active and quiescent, given by whether they are in the cell cycle or not, respectively. Single-cell RNA-sequencing data of the neural lineage shows a variation in gene expression among quiescent neural stem cells (qNSCs), suggesting the possibility of a continuum of qNSCs states in the transcriptome space. Inspired by this heterogeneity, we study the influence of the gene activation profile on the dynamics of neurogenesis using structured population models. To describe discrete and continuous transitions between cell states as well as the complicated underlying topological structure of the high-dimensional transcriptome space, we use structured population models on the space of Radon measures. Our model represents the qNSCs on a continuum from deep to shallow quiescence representing the pseudo-time axis that is often fitted to time snapshots of single-cell RNA sequencing data. Cells can move along this path and can be recruited to the compartment of active cells which proliferate. The cells resulting after division either differentiate into progenitor cells or return to quiescence. It is of particular interest to see how the additional structure from the continuity of the gene activation states of the quiescent neural stem cells influences the dynamics of neurogenesis. Namely, we study how cells move on the continuum, how the activation rate of the cells changes with the gene expression, and which genes a cell expresses upon its return to quiescence. Numerical simulations using a particle-based operator splitting algorithm allow us to investigate the influence of the state variable on the parameter functions as well as to study different hypotheses on the geometry of the state space. We also study the feedback mechanisms that regulate the parameter functions. This allows us to gain insights into the rules governing the system's dynamics.

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DEVELOPING REAL-TIME MODELLING CAPABILITIES FOR ANIMAL DISEASE OUTBREAK RESPONSE.

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Successful management of disease outbreaks requires deliberate and rapid response. As seen throughout the COVID-19 pandemic, mathematical modelling can provide important and novel insights from data as it gets collected, which provides an evidence base to support policy and decision-making. To improve modelling capability to support decision making in animal disease outbreak response in Australia, we are developing a suite of modelling workflows to estimate current spread and forecast future spread using outbreak data. We are also developing a range of decision-support workflows to improve how modelling can be used to support evidence-based policy. This poster will provide an overview of forecasting and modelling workflows and describe how we are using them as the basis of simulation exercise workshops. These workshops will provide important insights on the uptake of modelling to support decision-making.

THE ROLE OF INTERNAL AND EXTERNAL INTERPLAYS IN A SIR FORCED MODEL

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We investigated the behavior of a Susceptible-Infected-Recovered seasonally forced model for endemic childhood infectious diseases in the case where the target population is not isolated and, moreover, fast weekly fluctuations of the social contacts occur. We considered some key scenarios of interplay of Susceptible subjects with the external world, leading to subharmonic resonances and chaos. Our simulations suggest that the above–mentioned fast oscillations of the contact rate can cause the suppression/reduction of chaos and of subharmonic resonances. Thus, far from being filtered, they have an important role. If one considers an opposition of phase of the pattern of external infections w.r.t. the pattern of internal transmission rate, they result remarkably different from a scenario of synchrony. In most scenarios, the chaotic behavior is not associated to the phenomenon of the 'atom–infectious', i.e. the proportion of infectious is small but not unrealistic for large populations.

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FRACTIONAL DERIVATIVES TO MODEL VIROTHERAPY?

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Although not as well-known as the usual, integer order derivative, there exists a concept called 'fractional derivation'. As a matter of fact, the origin of fractional derivatives dates back to the same developmental period as that of regular derivation. As the name suggests, the introduction of a fractional derivative was hypothesised to generalise the order of a derivative to include non-integer, fraction or other, numbers.

In recent years, 'fractional mathematical oncology' has become more popular as an up-and-coming branch of mathematics that resorts to methods from fractional calculus to more accurately model various complex processes, such as tumour progression and virotherapy, related to cancer. One key advantage of this approach is the capability to incorporate memory effects of the underlying system into the governing equations. Furthermore, fractional derivatives are better suited to capture heavy-tailed distributions of events. For instance, the drug response of cancer cells within a tumour can exhibit high variability that is not merely random but often shows significant bias towards extreme responses.

Technically, starting from a basic one-dimensional continuous time random walk at the microscopic level, it is possible to derive, with the appropriate limits, both the usual and fractional versions of the macroscopic reaction-diffusion equation for the cell density. Different asymptotics of the probability density functions for the waiting time and jump length distributions lead to the Fourier-Laplace transform of the solution to the (fractional) reaction-diffusion equation, in the limit. In case of heavy-tailed waiting time and/or jump length distributions, anomalous diffusion is in reality better suited to describe movement than classical Brownian motion is. The main aim of this poster is to demonstrate how fractional differential equations naturally arise, starting from elementary assumptions and by going through the necessary derivations.

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DECIPHERING REGULATORY FEEDBACKS AMONG NEURAL STEM CELLS DURING NEUROGENESIS IN THE AGEING BRAIN

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Adult neurogenesis is the process through which mature neurons are generated from neural stem cells throughout adulthood. Neural stem cells (NSC) have the ability to self-renew to maintain the stem cell pool, as well as gradually differentiate into more specialized cell-types such as progenitors, neuroblasts and neurons.

In the adult brain, stem cells can be split into two subpopulations: a pool of active NSCs that are inside the cell cycle and actively divide into stem cells or to create more specialized cell types; and a subpopulation of quiescent NSCs "resting" outside of the cell cycle to protect themselves from mutations and which can be activated when needed. Existing mathematical models (see Danciu et al, 2023 for a review) describe the behaviour of NSCs via a system of ordinary differential equations representing the two NSC compartments, the dynamics of which is governed by parameters representing the activation rate of quiescent NSCs, the fraction of self-renewal and the proliferation rate of active NSCs. Experimental data suggests that model parameters are not constant and indeed, upon considering different scenarios of time-dependent parameters that may explain the data, Kalamakis et al. (2019) concluded that the most parsimonious model is that in which the activation rate decreases exponentially in time.

In order to understand the intrinsic properties of NSCs and their dynamics, we need to advance to non-linear models in which the system parameters are regulated by cells dynamics. We also extend the model to include all compartments of the neural lineage. Various scenarios of the dependence of system parameters on neural lineage sub-populations are considered, stemming from possible feedback signals among them. Mechanistic mathematical models can thus suggest what types of regulatory feedbacks can explain the behaviour observed in experimental data and help gain insights into the biology of neural stem cells and neurogenesis during ageing.

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QUANTIFYING THE COLLECTIVE BEHAVIOR OF CANCER CELLS: A NOVEL FRAMEWORK FOR ANALYZING CELL CLUSTERING AND THERAPY RESISTANCE

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Invasion into surrounding tissues and metastasis are critical hallmarks of cancer, as highlighted in seminal studies. Cancer cells exhibit invasion both as individual units and in collective groups, presenting significant challenges in therapeutic interventions. Particularly, collective clusters of cancer cells have been shown to exhibit resistance to radiotherapy and DNA damage, contributing to therapy resistance. In this context, we introduce a new framework designed to quantify the collective behavior of cancer cells using image data of nuclei and actin filaments at fixed time points. Building upon the concepts of cell graphs proposed in previous histopathology research, our approach constructs a mathematical graph based on the positional data of nuclei and actin filaments, extracted via the ImageJ analysis tool. In this graph, two nuclei are considered connected if they are nearest neighbors, facilitated by actin filaments, and their corresponding Voronoi cells are contiguous. We posit that this graph effectively encapsulates critical information for assessing cell clustering dynamics. Applying our methodology, we explored the collective behavior of melanoma cells subjected to the chemotherapeutic agent Doxorubicin, leveraging in vitro data obtained from collaborative research efforts. Preliminary analyses of the graph's observables—including the average number of neighbors and cluster coefficient values—indicate a notable increase in cell clustering following Doxorubicin treatment. This enhanced clustering suggests varying degrees and patterns of cell aggregation, which our framework proficiently identifies and quantifies. The overarching aim of our study is to uncover the signaling pathways that precipitate cancer cell clustering and consequent therapy resistance. By elucidating these pathways, our findings aspire to facilitate the development of targeted interventions to disrupt cell clustering, thereby augmenting the efficacy of cancer therapies.

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MATHEMATICAL MODEL OF ATOPIC DERMATITIS PATHOGENESIS

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Atopic dermatitis (AD) is a chronic inflammatory skin condition that impacts the quality of life of millions of people around the world. The pathogenesis of AD is determined by a complex interaction involving skin barrier, innate and adaptive immune responses, and skin microbiota. Transient environmental perturbations can trigger immune and tissue remodelling responses and these responses affect the skin barrier integrity making it more permissive for further environmental triggers to infiltrate, leading to AD symptoms. Characterizing the responses of the host to these perturbations is pivotal to uncover pathogenic mechanisms and improve strategies for diagnosis, prevention, and treatment of AD. This task is difficult to achieve from a purely empirical approach because these perturbations: (1) Often lead to synergic and non-linear responses that are hard to predict experimentally; (2) Can affect several regulatory processes that operate at different time scales simultaneously; (3) May result in symptoms that are clinically subtle; and (4) Can affect disease progression in a history-dependent manner. Here we propose a piecewise smooth mathematical model that couples three bistable motifs describing skin cell differentiation and the activation of innate and adaptive immune responses through slower tissue level variables representing barrier function, antimicrobial peptides, and pathogen loads. Mathematical analysis of this hybrid model has allowed us to: (1) Reproduce clinical observations of different disease courses of AD; (2) Characterize the effects of genetic and environmental perturbations on AD severity, and (3) Identify risk factors that increase the vulnerability to environmental aggressors. Our AD pathogenesis model is a tool to understand and simulate the progression and reversion of the disease.

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MODELLING COEVOLUTIONARY DYNAMICS IN HETEROGENEOUS SI EPIDEMIOLOGICAL SYSTEMS ACROSS SCALES

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We develop a new structured compartmental model for the coevolutionary dynamics between susceptible and infectious individuals in heterogeneous SI epidemiological systems. In this model, the susceptible compartment is structured by a continuous variable that represents the level of resistance to infection of susceptible individuals, while the infectious compartment is structured by a continuous variable that represents the viral load of infectious individuals. We first formulate an individual-based model wherein the dynamics of single individuals is described through stochastic processes, which permits a fine-grain representation of individual dynamics and captures stochastic variability in evolutionary trajectories amongst individuals. Next we formally derive the mesoscopic counterpart of this model, which consists of a system of coupled integro-differential equations for the population density functions of susceptible and infectious individuals. Then we consider an appropriately rescaled version of this system and we carry out formal asymptotic analysis to derive the corresponding macroscopic model, which comprises a system of coupled ordinary differential equations for the proportions of susceptible and infectious individuals, the mean level of resistance to infection of susceptible individuals, and the mean viral load of infectious individuals. Overall, this leads to a coherent mathematical representation of the coevolutionary dynamics between susceptible and infectious individuals across scales. We provide well-posedness results for the mesoscopic and macroscopic models, and we show that there is excellent agreement between analytical results on the long-time behaviour of the components of the solution to the macroscopic model, the results of Monte Carlo simulations of the individual-based model, and numerical solutions of the macroscopic model.

QUASI-STATIC APPROXIMATION MODELS IN ALZHEIMER'S DISEASE

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One of the most demanding challenges in mathematical modelling of Alzheimer's disease is to portrait the several time scales that occur in the progression of the pathology [2]. For this purpose, we adopt a quasi-static approach in our models, i.e. we identify at least one slow variable and one fast variable with the assumptions that the slow variable determines the whole evolution of the model and that the fast variable satisfies an equilibrium problem that depends on the slow one. Specifically, we select a weighted graph [2] as the spatial discrete domain. The fast variables are the concentrations of beta amyloid protein on the nodes, namely monomers, soluble polymers and plaques. They satisfy a set of ODEs on every node, equipped with spatial discrete diffusion and interactions between the three species (aggregation and fragmentation). However, the total mass is not conserved since we introduce a monomers' external source and the clearance process. The production of monomers depends on time through a probability measure f that describes the fraction of diseased neurons at every node [1]. It satisfies a transport PDE and naturally corresponds to the slow variable of the model. Since in the slow time scale the solution of the ODEs system reaches its steady state distribution instantaneously, the equation for f is coupled with the equations obtained imposing equilibrium on the ODEs. Ultimately, the beta amyloid system is coupled with the model in [2] requiring that the concentration of soluble beta amyloid and plaques influence the tau aggregation rate and its flux on the edges of the graph [3]. We provide existence for the beta amyloid equilibrium with the only assumption of positive clearance rates, a positivity property, numerical verification of the stability of the steady state and a dependence of the speed of convergence on the clearance rates, together with an existence result for the whole beta-tau system and numerical simulations on the human connectome.

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LIQUIDCNA++: TRACKING SUBCLONAL EVOLUTION IN LOW-QUALITY LIQUID BIOPSIES

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Liquid biopsies, DNA extracted from blood samples are revolutionising many areas of medicine, with an especially high impact on cancer research. In particular, low-pass whole genome-sequencing (lpWGS) of liquid biopsies makes quasi-real-time monitoring of the disease possible at minimal costs. LpWGS enables the sensitive detection of copy number alterations (CNAs), large-scale genomic alterations that are highly cancer-specific, and therefore provide a quantitative insight into the amount and composition of tumour-derived DNA within the blood. We previously developed liquidCNA [1] a bioinformatic method to track cancer composition from CNAs measured in liquid biopsies. However, liquidCNA can only provide robust results if at least - 10-15% of DNA comes from cancer cells - which is often not the case. Therefore, tracking how the tumour changes over time from cost-effective liquid biopsy sequencing remains a challenge.

Here we present a new in silico method to improve cancer-specific signal and cancer subclone tracking in liquid biopsy samples. We first leverage preliminary CNA calls from the highest tumour content sample (e.g. diagnostic biopsy) to identify the range of DNA fragment sizes enriched for tumour-derived DNA [2]. We then filter raw sequencing reads using this patient/experiment-specific fragment size range. Next, we apply a Bayesian Change Point detection algorithm [3] to binned read counts to call segment breakpoints and CNA values. Finally, tumour content and composition is evaluated collectively for all samples from the same patient using liquidCNA on the signal-enhanced CNA profiles.

We demonstrate the improved performance of each step and the pipeline on synthetically generated data sets and in vitro cell line mixtures. Overall, our method enables subclonal tracking even in samples with less than 3% tumour content, unlocking a high number of previously unusable liquid biopsy samples.

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MULTI-STRAIN DENGUE MODEL WITH SEASONAL FORCE

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Dengue fever is one of the endemic diseases in tropical countries and spreads rapidly during the rainy season due to the increasing abundance of its vector (Aedes aegypti mosquito). The recent data of ECDC (European Centre for Disease Prevention and Control) reported that dengue is starting to spread in Europe, in some regions of Italy. This vector carries four serotypes, namely DEN-1, DEN-2, DEN-3, and DEN-4, which can infect humans as the host population. Currently, there is no effective treatment to control the spread of the dengue virus. This research aims to focus on examining the interactions among these four serotypes within the human population by incorporating seasonal forcing into the SIR compartmental model. With these interactions, cross-reaction activities may be investigated, as well as the basic reproduction number of the strain. Simulations conducted will provide illustrations for various scenarios to understand the future disease behaviour of dengue fever based on the range of potential but realistic assumptions on the seasonal forcing.

EXPLORING REACTIVE EQUILIBRIA AND NETWORK PROPAGATION IN HOST-PARASITOID MODELS UNDER ON-OFF INTERMITTENCY

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Exploring the dynamics of host-parasite systems subject to environmental fluctuations, our research aims to investigate the dynamics of bursting behaviors modeled with on-off intermittency. Through the analysis of the interaction between environmental variability and trophic interactions, we explore ecological dynamics in both deterministic and stochastic scenarios. Our investigation focuses on a discrete Beddington-Free-Lawton model, where we introduce deterministic or stochastic perturbations that influence both grazing intensity and host population growth. In particular, we present numerical evidence of the reactivity of the free-parasitoid fixed point as a necessary condition for on-off intermittency, clarifying the transition from stable equilibria to chaotic regimes. Furthermore, our exploration extends beyond single-population scenarios to understand network-based interactions, revealing bursts of parasites not observable in isolated contexts. Our conclusions underscore the critical importance of carefully monitoring environmental variability to preserve ecosystem services and mitigate disruptions to trophic interactions, highlighting the potential of parasites as biological control agents amidst ecological fluctuations

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EXPLORING THE ROLE OF FITNESS FUNCTION OF EXTRACHROMOSOMAL DNA (ECDNA) IN CANCER EVOLUTION

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Extrachromosomal DNA (ecDNA), a circular DNA element, plays a crucial role in cancer development and heterogeneity. Its unique structure allows rapid and random segregation into daughter cells, leading to rapid changes in copy number. Tumor cells harboring ecDNA often exhibit heightened aggressiveness and enhanced fitness. However, the extent to which cellular fitness depends on ecDNA copy number remains poorly understood due to the scarcity of theoretical models addressing this relationship.

In contrast to existing models neglecting copy number dependency, we propose utilizing a sigmoid equation as a fitness function to investigate the evolutionary dynamics of ecDNA in cancer cell populations experiencing positive selection. We employ stochastic simulations and propose theoretical experiments involving single-cell sampling to explore the dependency of cellular fitness on ecDNA copy number. Additionally, we utilize approximate Bayesian inference to estimate parameters of the fitness equation.

The presence of the fitness equation leads to a bimodal distribution of ecDNA in cancer cell populations under specific parameters. Theoretical experiments using single-cell sampling reveal variations in tumor cell growth time and ecDNA distribution, which might provide theoretical support for its existence. Furthermore, parameter estimation employing the ABC algorithm suggests ideal inference for the initial number of ecDNAs and the fitness equation model. Our theoretical framework offers valuable insights into verifying copy number-dependent fitness equations and understanding the evolutionary dynamics of ecDNA. These findings hold promise for validation in real experiments, providing crucial insights into ecDNA evolution dynamics.

A GROWING DOMAIN PDES MODEL OF HORMONE FEEDBACKS IN THE SHOOT APICAL MERISTEM OF PLANTS

Filip Klawe (Institute of Mathematics, Heidelberg University)

We will present a mathematical framework for a model consisting of the partial differential equations (PDEs) defined on the moving domain. The model is based on a simplified (2D) geometry and the domain changes uniformly in all directions. The model has been applied to describe the evolution of the chemical signals and the size of the shoot apical meristem (SAM) of arabidopsis thaliana.

The model consists of two ordinary differential equations (ODEs) describing the evolution of domain radii: the first one is the radius of the whole domain and the second one is a radius of the organising centre. The functions describing these evolutions depend on the concentrations of chemical signals within the (moving) domain. The signal concentrations are described by a system of PDEs and depend on the values of the radii. This leads to a coupled problem between the PDEs and the deformation of the domain.

The model provides new insights into the approach used to describe the growth/decay of SAM. In contrast to previous work, we assume that the growth of SAM is a consequence of local cell division. Local cell division is a consequence of local concentrations of chemical signals. To work with a simplified two-dimensional disc geometry of the shoot apical meristem (SAM), the geometry of the SAM is given by its radius.

We prove the existence and uniqueness of the solution. We also provide the results of numerical experiments by simulating perturbations in the levels of key transcription factors that maintain SAM homeostasis. The new approach allows us to capture larger changes in the SAM radius. In addition, the results of the long-term behaviour of the perturbation experiments provide results that are more consistent with biological observations.

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QUANTIFYING MASSIVELY PARALLEL MICROBIAL GROWTH WITH SPATIALLY MEDIATED INTERACTIONS

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Quantitative understanding of microbial growth is an essential prerequisite for successful control of pathogens as well as various biotechnology applications. Even though the growth of cell populations has been extensively studied, microbial growth remains poorly characterised at the spatial level. Indeed, even isogenic populations growing at different locations on solid growth medium typically show significant location-dependent variability in growth. Here we show that this variability can be attributed to the initial physiological states of the populations, the interplay between populations interacting with their local environment and the diffusion of nutrients and energy sources coupling the environments. We further show how the causes of this variability change throughout the growth of a population. We use a dual approach, first applying machine learning regression models to discover that location dominates growth variability at specific times, and, in parallel, developing explicit population growth models to describe this spatial effect. In particular, treating nutrient and energy source concentration as a latent variable allows us to develop a mechanistic resource consumer model that captures growth variability across the shared environment.

As a consequence, we are able to determine intrinsic growth parameters for each local population, removing confounders common to location-dependent variability in growth. Importantly, our explicit low-parametric model for the environment paves the way for massively parallel experimentation with configurable spatial niches for testing specific eco-evolutionary hypotheses.

Z-TYPE CONTROL ACTIONS TO MITIGATE THE NEGATIVE EFFECTS OF EASTERN COTTONTAIL INVASION IN ITALY

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Alien species cause ecological disruptions, alteration of native population dynamics and ecosystem dysfunctions. The negative effects can be exerted demographically, by competition, predation and hybridization, or epidemiologically, via disease transmission. We consider the specific invasion situation concerning the eastern cottontail (Sylvilagus floridanus) in some regions of Italy. Affecting the local predator-prey dynamics, this invasion has shifted the natural equilibrium between the native European hares (Lepus europaeus) and red foxes (Vulpes vulpes), since apparent competition mechanisms exist between the two lagomorphs. In this framework, we investigate the situation intending to mitigate the negative effects of the invasion. For this task, we apply Z-type control considering three possible alternatives to act on a three-population reference model, in order to possibly give indications to ecosystem managers. At first, we consider indirect control on the cottontails by removing predators or importing new individuals of the native prey population. Then, we combine indirect control on cottontails, acting on foxes, and direct control on hares.

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BRANCHING PROCESSES FOR MODELING RECONSTRUCTED PHYLOGENETIC TREES

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Stochastic models for phylogenetic trees are still not well understood. Whilst an array of stochastic processes (e.g. birth-death processes and the coalescent) are frequently used, a large class of them fit empirical phylogenetic trees poorly. Age-dependent speciation/extinction models have been shown to explain data better but have long been considered intractable. Here, we show that, at least mathematically, this is not so. Inspired by its application in phylogenetics, we define and study a reduced time-varying Bellman-Harris process and the related reduced branching tree, representing respectively the counting process of the number of lineages through time and the reconstructed phylogenetic tree with observed speciation times. A full distributional characterization of this process and its reduced tree are given through a set of integral equations, whose solutions are simple to approximate numerically. The joint distribution of the tree shape and the observed speciation times characterized, allow for maximum likelihood estimation of evolutionary dynamics given a reconstructed phylogenetic tree.

MULTISCALE HYBRID CONTINUOUS MODEL OF HUMAN BLOOD CIRCULATION IN INJURY

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Local vascular injury leads to change of rheological conditions in all the remaining intact circulation, which in its turn determines boundary conditions in the pathology region. Quantitative description of the hemodynamic changes and the mechanisms underlying them are needed. Our aim was to develop mathematical model to investigate change in blood flow both in the region of pathology and in all the remaining intact vessels in a human circulatory system. We built a multiscale stationary hemodynamic model to simulate changes in pressures and fluxes in the human upper limb circulation due to venipuncture. Blood was simulated as an incompressible Newtonian fluid flowing through rigid cylindrical vessels exposed to a constant pressure difference as boundary conditions. The injury region was resolved in 3D, where Navier-Stokes and continuity equations are solved numerically. The rest of the vessels were represented implicitly using a system of linear equations based on the Hagen-Poiseuille's law. For smaller radius of wound (RW) below the critical value of 320 um, the rate of blood loss (BL) was determined by the hydrodynamic resistance of the wound itself and increased with RW according to sigmoidal law. For RW above threshold of 320 um, BL was controlled by the hydrodynamic resistances of the adjacent vessels (AV) and did not depend on RW. The blood flows in AV were dependent on RW in the same way as BL. The pressure in every bifurcation of the circulation system was decreasing function of RW and depended on RW according to the sigmoidal law. The amplitude of that decrease of pressure (DP) was higher for the bifurcations located closer to the damaged vessel. The DP at any bifurcation depended on the resistance of the diverting adjacent vessel. The bigger the resistance was, the bigger was the pressure drop.

A DEEP-LEARNING APPROACH TO THE STUDY OF BACTERIAL GROWTH AND GENE EXPRESSION IN QUORUM-BASED SYSTEMS.

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factors related to cell replication are different cell-to-cell. Often, quantifying these effects require a experimental micro-well setup that is difficult to build and can be expensive in developing countries. Few models have tried to explain this phenomenon on a single-cell scale, however, a quorum-based approach has not been fully studied [1]. We developed a Neural Network-based algorithm that can allow us to track differences among cells, not only in sizes but also in growth rates. Growth rates are usually quantified at a population level, but there is a lack of data related to stochasticity of growth rates, and it is particularly challenging when examining culture media that can induce drastic changes in cell size, like antibiotics. Since cell growth is known for affecting gene expression levels and noise in gene expression, using our algorithm and experimental data, we found theoretical changes in the expression of a constitutive gene with the application of antibiotics, particularly in the extrinsic sources of noise. This could allow us to delve into the consequences of the usage of antibiotics in non-genetic cell variability that can induce phenotypic changes in fluctuant and harmful environments, like antibiotics. Understanding this relationship is crucial to understand gene expression under stressful conditions, and particularly gene expression near the turning point into the persistent state. It is well described that persistence heighten the probability of bacteria of becoming resistant. Describing gene expression under the influence of antibiotics can be very useful to understand how transcription networks and metabolism behave in this changing phase. This approach uses a U-Net convolutional neural network to segmentate bacteria individually and collectively which allows us to keep track of the changes in area and fluorescence which is an indicative of gene expression.

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DIFFERENTIATED ELEMENTARY MODES REVEAL METABOLIC SHIFTS

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Enzyme constrained (EC) metabolic models have increasingly been used over the past several years to make empirically observed predictions about cell metabolism. We identified similarities in elementary flux modes in the optimal solutions of over 300 EC models of yeasts, and differentiated the proportion of flux through these modes required for optimal biomass production. Similar to Metabolic Control Analysis (MCA), this predicts the control of a single step on whole cell metabolism.

We have built upon the result from de Groot [1] that an optimal solution to an EC model with n enzymatic constraints will have n elementary flux modes (EFMs). We calculate the contribution of these EFMs to the total biomass production of the solution. This proportion of EFM usage is differentiated to reveal shifts in metabolism resulting from changes in enzyme parameters.

Differentiating the proportion of EFM usage in an optimal solution can guide metabolic engineering by providing a list of candidate enzymes that are critical for the enhanced production of a target compound. In modelling pathogenic metabolism, one can use this technique to search for potential drug targets that have a large effect on metabolic strategies.

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COST-EFFECTIVE BOOSTING IN THE POST-OMICRON ERA OF COVID-19 MANAGEMENT

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As COVID-19 transitions from the pandemic phase to endemic circulation, populations now have a wide range of exposure and vaccination histories, resulting in heterogeneous immune landscapes. This is due to both multiple rounds of vaccination and widespread exposure, particularly to highly infectious Omicron lineage variants. Social mobility restrictions have been relaxed, leaving us to rely on population immunity to control transmission and disease impacts. Careful consideration of optimal vaccine use is required through this next phase of COVID-19 management to cost effectively minimise the burden of disease.

We simulated four linked models: immunological, transmission, clinical pathways and cost effectiveness. Using this pipeline of models, we simulated a range of immune landscapes based on population characteristics and diverse vaccine and infection histories. We assessed the impact and cost effectiveness of alternative COVID-19 vaccination strategies on infections, hospitalisations and deaths. Across different population demographics and income levels, we consistently found that annual elder-targeted boosting strategies are most likely to be cost-effective, with paediatric programs unlikely to be cost-effective. Half-yearly boosting may only be cost-effective in populations with older demographics and higher cost-effectiveness thresholds. These results provide evidence of the value for money of continued booster vaccination to protect against severe COVID-19 disease outcomes across both high and low-middle income settings and show that the biggest health gains are made by targeting older age-groups.

ANALYSING THE DYNAMICS OF SCRNA-SEQ DATA WITH MARKOV CHAINS.

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Advances in single cell RNA sequencing technologies allow us to measure gene expression at a global scale in many individual cells. This data motivates researchers to develop mathematical and statistical methods to extract any and all information from this snapshot data due to the large significance of understanding gene regulation. Methods such as RNA velocity take advantage of the spliced and unspliced information to construct dynamics useful for downstream analysis. We have taken on the problem of inference of dynamics of cell differentiation without using RNA velocity but by considering the data to have been generated by a homogenous SDE with bounded variation: and from this assumption constructed a Markov Chain (MC) on the data in such a way to imply a dynamic on the underlying manifold. Our approach extends the current graph construction methods such as Diffusion Pseudotime (DPT). From this we can extract pseudotime, velocity estimates, terminal states, decision boundaries, as well as cheaply sample cell trajectories and measure their ensemble gene expression as they differentiate. We validate and benchmark our method in comparison to other approaches on toy SDE models of the transcription-splicing process, where the ground truth is known, to evaluate the fidelity of our results.

STOCHASTIC MODELS OF REGULATION OF TRANSCRIPTION IN BIOLOGICAL CELLS

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We study an important global regulation mechanism of transcription of biological cells using specific macro-molecules, 6S RNAs. The functional property of 6S RNAs is of blocking the transcription of RNAs when the environment of the cell is not favorable. We investigate the efficiency of this mechanism with a scaling analysis of a stochastic model. The evolution equations of our model are driven by the law of mass action and the total number of polymerases is used as a scaling parameter. Two regimes are analyzed: exponential phase when the environment of the cell is favorable to its growth, and the stationary phase when resources are scarce. In both regimes, by defining properly occupation measures of the model, we prove an averaging principle for the associated multi-dimensional Markov process on a convenient timescale, as well as convergence results for "fast" variables of the system. An analytical expression of the asymptotic fraction of sequestrated polymerases in stationary phase is in particular obtained. The consequences of these results are discussed.

DESIGNING A CONSUMER-RESOURCE MODEL FOR UNDERSTANDING INTERACTIONS IN COMPLEX MICROBIAL COMMUNITIES

Jannis Fabian Pohlkotte (Heinrich Heine University Düsseldorf)

Mathematical modelling of microbial communities is essential for understanding interactions between their members, the process of community assembly and what determines the dynamics, stability and composition of a microbiome. MacArthur consumer-resource models describe simple communities driven by competition for resources [1]. Expanding this framework to include the exchange and consumption of metabolites enables modelling microbial communities and explaining community assembly, taxonomic composition and the structure of the metabolic network of a system [2]. A commonly used approach assumes a base metabolism where the only differences between species are their resource uptake preferences [2]. Here, we expand upon these microbial consumer-resource models with the goal of creating a more mechanistic and biologically interpretable framework. Metabolic processes are designed to incorporate enzyme kinetics while ensuring the validity of mass and energy balances. This approach allows microbial communities to be modelled on a flexible scale between two extremes: Firstly, treating each species as a black box where the entire metabolism is summarized as one metabolic macro-reaction, which requires only a small amount of knowledge of the species, and secondly, modelling each part of a species' metabolism as a separate process which allows a more accurate and in-depth look at a microbial community and the exact interactions, but requires large amounts of knowledge and data. We show that this model can exhibit a wide range of behavioural patterns and reproduce findings of previous works. We demonstrate that this model can be applied to simple systems consisting of two bacterial species, algal-bacterial communities, and more complex communities containing the alga Chlamydomonas reinhardtii, the fungus Verticilium dahilae and a number of different bacteria.

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IDENTIFICATION OF NEW ANTIFUNGAL TARGETS IN ASPERGILLUS USING GENOME-SCALE METABOLIC MODELLING

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Infections caused by common pathogenic fungi in humans result in over 1.5 million deaths worldwide every year. One of the most prevalent sources of infection is the airborne saprophytic fungus Aspergillus fumigatus. The increasing emergence of strains resistant to known antifungal agents is a major concern, which justifies looking for and targeting new mechanisms important for fungal pathogenicity and survival. Carbon acquisition and further metabolic processes play an important role in fitness and survival of the fungus, consequently it is important to explore the ways that A. fumigatus metabolism can be targeted.

We used the pan-genome-scale metabolic model for Aspergillus fumigatus [1] as a platform for identifying novel antifungals by targeting essential genes for fungal growth. In vitro growth of the fungus was simulated using Flux Balance Analysis [2], by setting the objective function of the model to biomass maximisation. After applying experimental media conditions, 71 genes were identified as essential to sustain growth. These genes were searched for in the KEGG Orthology (KO) database and excluded if a human gene was found in the gene's KO group. This produced a reduced list of 21 candidate genes, which had no functional ortholog in the human genome. Using the KO groups and several pharmacology databases, six drug candidate genes were found which are non-human functional orthologs and could potentially be targeted by existing drugs. Drug simulations were performed to determine the effect of inhibiting these genes on fungal growth. For all drug candidates, decreased permitted flux correlated with decreased growth, confirming that inhibition of these reactions leads to reduced fungal survival. These reactions were involved in either folate biosynthesis or pyrimidine, phenylalanine, tyrosine and tryptophan metabolism, suggesting these pathways are key targets for the development of new antifungals.

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GENERAL PROTOCOL FOR PREDICTING OUTBREAKS OF INFECTIOUS DISEASES IN SOCIAL NETWORKS

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Epidemic spreading on social networks with quenched connections is strongly influenced by dynamic correlations between connected nodes, posing theoretical challenges in predicting outbreaks of infectious diseases. The quenched connections introduce dynamic correlations, indicating that the infection of one node increases the likelihood of infection among its neighboring nodes. These dynamic correlations pose significant difficulties in developing comprehensive theories for threshold determination. Determining the precise epidemic threshold is pivotal for diseases control. In this study, we propose a general protocol for accurately determining epidemic thresholds by introducing a new set of fundamental conditions, where the number of connections between individuals of each type remains constant in the stationary state, and by devising a rescaling method for infection rates. Our general protocol is applicable to diverse epidemic models, regardless of the number of stages and transmission modes. To validate our protocol's effectiveness, we apply it to two widely recognized standard models, the susceptible–infected–recovered-susceptible model and the contact process model, both of which have eluded precise threshold determination using existing sophisticated theories. Our results offer essential tools to enhance disease control strategies and preparedness in an ever-evolving landscape of infectious diseases.

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MULTI-RESOLUTION MODELLING OF INTRACELLULAR ION DYNAMICS

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Understanding ion dynamics is important for many biological processes, including muscle contraction, neuronal excitability and intracellular signal transduction. I will discuss two types of spatio-temporal models of ion dynamics inside cells: (i) macroscopic (mean-field) description given in terms of the Poisson-Nernst-Planck (PNP) partial differential equations (PDE) system describing the time evolution of concentrations of ions and electrostatic potential; and (ii) microscopic description written in terms of the Brownian dynamics simulations of individual ions. Starting with the microscopic model, its macroscopic description is first derived as a system of PDEs. This derivation is then used to develop a multi-resolution simulation method, which uses detailed Brownian dynamics description in localized regions of particular interest (in which accuracy and microscopic details are important) and a (less-detailed, coarser) macroscopic model in other regions in which accuracy may be traded for simulation efficiency. The resulting multi-resolution simulation method provides a generalization of the PDE-assisted Brownian dynamics algorithm (used for reaction-diffusion systems of uncharged particles) to Brownian dynamics simulations of ions. The accuracy of the derived macroscopic PDEs and multi-resolution methods is demonstrated using illustrative 3-dimensional Brownian dynamics simulations with sodium and chloride ions.

EFFECTS OF NONLINEAR MEMBRANE CAPACITANCE IN THE HODGKIN-HUXLEY MODEL OF ACTION POTENTIAL ON THE SPIKE TRAIN PATTERNS OF A SINGLE NEURON

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The membrane capacitance has been shown to have a nonlinear dependence on the cell membrane potential in various types of cells. But the role of the nonlinear membrane capacitance in neurons has not been studied in detail. Herein, by considering the membrane capacitance to be a nonlinear parameter, we have explored the behavior of the cell membrane in three different types of neurons, i.e., squid giant neuron, rodent hippocampal interneuron, and rodent cortical neuron. The Hodgkin-Huxley equation of action potential was modified accordingly and simulated computationally. Our simulated results suggest that the action potential amplitude of a neuron almost remains the same for some duration when the voltage dependence parameter of the nonlinear capacitance increases up to a certain range, the initiation of the next action potential is delayed and the reduction in spike frequencies occurs in comparison to constant membrane capacitance. This indicates the importance of nonlinearity in membrane capacitance. Simultaneously the inter-spike interval (ISI) changes with the nonlinear membrane capacitance parameter. The gating dynamics show changes mainly in the Na+ activation current while the membrane capacitance is considered to be nonlinear. The above-mentioned computational results are primarily predictive pending experimental verification.

HYBRID MODELS FOR RECONSTRUCTION AND MODELING OF SIGNALING NETWORKS

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Modeling of molecular interaction networks represents a powerful tool to improve our understanding of the complex regulatory mechanisms inside cells. Uncovering the still widely unknown factors behind cellular states and responses brings us closer to the ideal of personalized treatments for a more efficient medicine.

A crucial step in the modeling process is the identification of the network components that serve as the "scaffold" of the model. These are often built from literature, from mathematical or statistical relations found on experimental data, or from combinations of both. While several methods and advances have been presented, network reconstruction remains an open question and an active area of research.

In this project we aim for the development of a hybrid approach integrating machine learning based analysis with mechanistic, equation based knowledge. Our goal is, on the one hand, to engineer a modeling pipeline that improves explainability and robustness of current reconstruction methods; on the other, the implementation of a model that leverages the advantages of both, so called "white and black box" approaches, for prediction under untested conditions.

As a use case, we study signaling networks from static, combinatorial phosphoproteomics data under perturbations. The method relies on the identification of patterns from multi-variate stimulation screenings and their changes under inhibition with graph substructures [1][2], deriving on a transport network with parametric and non-parametric models at the nodes for prediction of phosphorylation values.

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IDENTIFICATION OF NEW DRUGGABLE TARGETS IN CHROMATIN REMODELING-DEFICIENT TUMORS COMBINING MULTI-OMICS ANALYSIS, BIOINFORMATICS AND SYSTEMS

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Approximately 20% of human solid tumors are mutated in genes encoding subunits of the SWI/SNF complex, a chromatin remodeling machinery. Most SWI-SNF mutated malignancies are resistant to conventional chemotherapy, and the identification of novel drug targets and effective synergistic combinations are urgently needed. To that end, we investigated the molecular landscape of HAP1 isogenic cell lines, mutated for single SWI-SNF genes, or other chromatin remodelers, through transcriptomics, proteomics, and high-throughput drug screening. Both differential gene expression analysis and pathway enrichment investigation, achieved through an optimized bioinformatics pipeline, concluded an inconstant correlation between dysregulated genes/pathways at the gene and protein expression levels. Unexpectedly, the Metabolism of proteins pathway category was the most dysregulated one in SWI/SNF KO lines. Three chemicals emerged as selectively cytotoxic for HAP1 SWI/SNF-mutant cell lines. A pipeline was developed to map cytotoxic drugs to genes interacting with them, in order to integrate proteomics, drug screening and CRIPSR data from the DEPMAP public database. Data integration identified several synthetic lethal hits, including one superhit that was revalidated in preclinical models. The next step is to build a systems pharmacology ODE-based model based on CRISPR or drug-screening protein targets and informed by proteomics data, to predict optimal drug combinations against SWI/SNF-deficient tumours.

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SEASONAL VACCINATION STRATEGY: A PHASE CONTROL APPROACH

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In the context of epidemiology, chaos is often regarded as an undesirable phenomenon associated with the unpredictability of infectious diseases. As a consequence, the problem of converting chaotic motions into regular motions becomes particularly relevant. In this article, we consider the so-called phase control method applied to the seasonally forced SIR epidemic model to suppress chaos. Interestingly, this method of controlling chaos has a clear meaning as a weak perturbation on a seasonal vaccination strategy. Numerical simulations show that the phase difference between the two periodic forces - contact rate and vaccination - plays a very important role in controlling chaos.

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ELUCIDATING VESSEL CO-OPTION RESISTANCE IN GLIOBLASTOMA: A COMPREHENSIVE TRANSPORT MODEL FOR NESTIN EXPRESSION DYNAMICS

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Glioblastoma (GBM), the most prevalent primary brain tumor in adults, is associated with a particularly dismal prognosis despite advances in treatment strategies. This is reflected in a median overall survival of less than two years [1]. GBM exhibits considerable resistance to various therapeutic approaches, a situation that has seen little improvement over the past two decades. This resistance is attributed, in part, to its extensive cellular heterogeneity and the complex interactions between tumor cells and their microenvironment, including the brain parenchyma and the immune system. Recent research has uncovered a reprogramming phenomenon whereby GBM cells transition into a vessel-co-opting invasive state [2]. This adaptability, inherent in naive cell populations, may also be induced by therapeutic interventions. Set along the proneural-mesenchymal axis, this state is distinguished by its resistance to therapy, among other features. Nestin, an intermediate filament protein, has emerged as a pivotal marker in this context.

In our study, we have developed a transport system using partial differential equations to simulate the evolution of Nestin expression under a variety of treatment scenarios, thereby extending previous models [3]. This approach allows us to distinguish between cellular reprogramming (alterations in cellular phenotypes regarding Nestin expression) and Darwinian selection within the GBM population. This conceptual framework elucidates the dynamics that govern the transition from lower to higher levels of Nestin expression. Our model accurately captures the underlying processes that drive this marker throughout the considered experimental timeframe (7 days) following radiation administration across a range of dosages (2-12 Gy), including the control group. Our main goal is to use this model to improve treatment strategies for better survival and to identify key characteristics for targeted drug development.

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DYNAMICS AND OPTIMAL TREATMENT SCHEDULE IN NEUROBLASTOMA USING ONCOLYTIC VIRUSES: A MATHEMATICAL PROOF OF THE EFFICACY OF CELYVIR

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This poster presents the results of a study investigating the efficacy of Celyvir, an innovative therapeutic approach integrating mesenchymal stem cells (MSCs) and the oncolytic virus ICOVIR 5, in the treatment of neuroblastoma. Using mathematical modelling and numerical simulations, two treatment modalities, continuous and periodic, were explored. The analysis revealed response patterns suggesting that Celyvir has the ability to both accelerate tumour progression and induce remission. In addition, evaluation of optimal control strategies demonstrated efficacy in reducing tumour burden and treatment costs while slowing tumour expansion beyond critical thresholds. Furthermore, the identification of a viral load critical for treatment success underscores the need to maintain optimal viral levels to prevent neuroblastoma recurrence. Overall, the findings suggest the effectiveness of a periodic bang-bang regime in optimizing Celyvir therapy, offering insights for enhancing cancer treatment outcomes.

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PARAMETER OPTIMIZATION OF PHASE-FIELD MODELING BASED ON EXPERIMENTAL IMAGE DATA OF CELL ARRANGEMENTS

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Geometric effects of cells and cellular environments can play a significant role in determining cell fate, cell mobility, and intra-/inter- cellular dynamics. Nevertheless, conventional mathematical modeling approaches to understand cellular geometry effects have long been based on conceptual descriptions such as artificial spheres or ellipsoids. Recently, a new modeling approach using the phase-field method combined with actual image data has been proposed, demonstrating the importance of using data to understand and discover unknown or overlooked mechanism in cell arrangements [1]. Therefore, in this study, we aim to develop a universal data-combined mathematical tool by which we can combine "cell's actual parameters" based on "real image data" of cells with phase-field modeling describing cell arrangements. To address this, we propose a new parameter optimization method using experimental image data of C. elegans embryos in early development stage. This method also allows us to achieve feedback information on the physical characteristics for each cell from the data, providing biological insights into the overall dynamics of the cell arrangements. Our data-combined mathematical method is species-independent of the biological models and can be applied to other biological system.

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TIME FILTERING METHOD FOR A TRAFFIC FLOW MODEL INSPIRED BY DNA TRANSCRIPTION MODELING

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The focus of this presentation is the development, numerical simulation and parameter analysis of a model of the transcription of ribosomal RNA in highly transcribed genes. Inspired by the well-known classic traffic flow model Lighthill-Whitham-Richards (LWR), a non-linear advection continuum model is used to describe the DNA transcription process. Recently combining time filtering process with fully implicit schemes for nonlinear problems has shown increase accuracy with minimal modifications to existing code. The numerical treatment presented for LWR model simulations includes introducing a low complexity and time accurate method by adding a simple linear time filter to explicit and implicit finite difference schemes. This improved new method is modular and requires a minimal modification of adding only one line code resulting in increased accuracy without increased computational expense.

PUBLIC RELATIONS STRATEGIES FOR THE NON-SCIENTIFIC COMMUNITY IN MATHEMATICAL AND THEORETICAL BIOLOGY RESEARCH

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Communicating research to the non-scientific community, especially to young people, is an important issue in educating the next generation in the mathematical sciences. Today, young people use a wide variety of media on a daily basis, and traditional press release publicity alone is not sufficient in some respects. In this issue, I would like to present a new approach my laboratory has taken to disseminate our research on SARS-CoV-2. This involves two strategies that combine press releases and youth-oriented content. In press releases, it is essential to work with newspaper reporters and illustrators to ensure accurate and prompt dissemination of information. In addition, in order to attract the attention of young people, it is necessary to utilize the media with which they are usually in contact to resolve the difficult images of mathematical models and computer simulations in an easy-to-understand, visual manner. To achieve this, we will develop an extensive PR strategy utilizing SNS, including YouTube, VTuber, and Metaverse. In addition, our social PR strategy for youth has two main pillars: common language and stakeholder management. In Common Language, the goal is to chew up jargon and visualize scientific concepts in a way that is easily understood by the non-scientific community. Stakeholder management, on the other hand, involves not only communicating information, but also building mutually beneficial relationships with target audiences and media personnel to create an open and interactive community. These strategies are essential for communicating the complex concepts and data of the mathematical sciences to a broader audience, especially the next generation of young people, in a way that is easy to understand.

MODELLING G PROTEIN-COUPLED RECEPTORS (GPCRS) COMPARTMENTALIZED SIGNALING

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G protein-coupled receptors (GPCRs) are membrane receptors that play a pivotal role in the regulation of reproduction and behavior in humans. They exhibit dynamic trafficking between intracellular compartments and the plasma membrane, activating distinct signaling pathways in each location. As we advance our ability to measure signaling activity within intracellular compartments, a quantitative framework becomes essential to understand these phenomena's interplay.

We propose a model for compartmentalized signaling based on a piecewise deterministic Markov process (PDMP). The stochastic part of the model accounts for formation, coagulation, fragmentation and recycling of intracellular vesicles which contain the receptor, whereas the deterministic part of the model represents evolution of chemical reactions due to signaling activity of the receptor. We are interested in the existence and convergence to a stationary measure. We are able to obtain results in this direction under two sets of assumptions on the deterministic flow : global exponential contractivity or conservation of chemicals quantities.

Furthermore, we conducted Bioluminescence Resonance Energy Transfer (BRET) experiments under various conditions to longitudinally measure GPCRs trafficking and signaling. We utilized these data to fit a simpler ODEs model of the BRET protocol and GPCRs activity.

STUDYING THE GROWTH AND INTERNAL COMPOSITION OF CHLORELLA VULGARIS THROUGH MECHANISTIC MODELS

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Microalgae are a promising renewable raw material for a wide range of applications, such as food, feed, fertilizers, and biofuels. Their production promises to solve environmental issues, such as greenhouse gas emissions, scarcity of arable land and sustainability impacts of agriculture, and depletion of fossil raw materials.

To overcome current bottlenecks in microalgae cultivations, biomass production needs to be optimized and the desired compound in the biomass, such as lipids for fuels, proteins for food or carbohydrates for bioethanol, maximized. Algae are complex biological systems and the optimization of the growth parameters towards these goals is not straightforward.

The present study aims to formulate a mechanistic model based on Ordinary Differential Equations (ODEs) that explains growth and internal composition of the microalga Chlorella vulgaris, widely studied for its capacity to accumulate lipids. In this case, the biomass and the internal accumulation of carbohydrates, lipids, proteins, and pigments represent states of the system, and their temporal evolution is expressed as a function of nutritional regimes and CO2 supplementation. The algae are cultivated in photobioreactors with artificial lighting and injection of CO2-rich gas streams, under changing nutritional conditions in terms of nitrogen and phosphorous availability. Periodic sampling to assess growth and biomass composition provides the experimental data necessary to fit model parameters in a meaningful way. The development of this model relating growth and internal composition with external inputs lays the foundation for feedback control and online optimization of the cultivation and enhance the applicability of microalgae in the field of industrial biotechnology.

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ANALYSIS OF A SIZE-STRUCTURED FISH OOCYTE POPULATION MODEL

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We introduce and analyze a size-structured oocyte population model, with non local nonlinearities on recruitment, growth and mortality rates to take into account interactions between cells. We pay special attention to the form of the recruitment term, and its influence on the asymptotic behavior of the cell population. This model is well-suited for representing oocyte population dynamics within the ovary. Nonlocal nonlinearities enable us to capture the diverse feedback mechanisms acting on the growth of oocytes of varying sizes and on the recruitment of new oocytes. We investigate existence and uniqueness of global bounded solutions, as well as the asymptotic behavior of the model. Under an additional assumption regarding the form of the growth rate, we can reduce the study to that of an equation with linear growth speed and nonlinear inflow boundary condition. Investigation of steady-states local stability can be done. In some biologically interesting cases, some explicit calculations are carried out, and we are able to explore Hopf bifurcation existence.

BIOMECHANICAL CONTROL OF ACTIVITY AND TRANSMISSION OF INFORMATION IN THE CELL NUCLEUS

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Recent findings suggest that the biomechanical properties of cell nuclei significantly influence their biological activity [1]. This is because they act as modulators of matter and energy transport phenomena. Numerous studies have demonstrated a direct relationship between viscoelastic properties and metabolic status or physiological disorders. Furthermore, the formation of small domains with highly correlated dynamics has been observed, controlled by local rigidity and nuclear activity [1].

Can these domains be interconnected through the elastic elements linking them? Is it possible to interpret nuclear dynamics as the dynamics of weakly interconnected domains capable of transmitting mechanical information beyond local constraints imposed by viscous dissipation?

To explore these questions, we propose modeling the stochastic intranuclear dynamics using graph theory. HUVEC, serving as biological models, have been observed with high-resolution spatiotemporal microscopes. The dynamics of local chromatin domains, derived from PT trajectories, have been used to construct graphs, where vertices represent the observed domains and edges represent the connectivity networks between them. The edge weights are determined by the inverse of the distance and correlation between domains. We tested two different biological scenarios: living cells in complete cell culture environments and cells fixed with paraformaldehyde.

The efficiency of the hypothetical chromatin network was measured in terms of graph betweenness centrality in these two extreme scenarios. These measurements were then correlated with mechanical features (like local rigidity, diffusion coefficient and viscosity) and activity indicators (such as spectral entropy and physical entropy production). Comparing living and fixed cells, we observed a higher number of nodes with significant betweenness centrality in living cells. This implies that chromatin domains are more interconnected in living cells.

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A MINIMAL MODEL COUPLING COMMUNICABLE AND NON-COMMUNICABLE DISEASES

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Non-communicable diseases (NDCs) are very common and, therefore, play a key role in the epidemiology of communicable or infectious diseases (CD) [2]. The aim of this work is to analyze the interplay between NCDs and CDs. A model combining the simplest communicable and non-communicable disease models is analyzed. We assume that individuals affected by the NCD are somehow weaker to face the CD, introducing basal heterogeneity in populations where communicable diseases evolve. Our results [1] show that considering the non-communicable disease allows the communicable disease to become endemic even if the basic reproduction number is less than 1. This feature is known as subcritical bifurcation. An important aspect of the model proposed here is its ability to undergo a subcritical bifurcation while not incorporating any of the mechanisms analyzed in previous studies. Furthermore, if the non-communicable disease is not explicitly considered results in overestimating the reproduction number and, thus, giving wrong information about the actual number of infected individuals. We also calculate sensitivity indices and derive information to avoid the CD to become endemic. We found that sometimes it is worth to act on more than one coefficient of the model at once.

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TILING MECHANISMS OF THE COMPOUND EYE THROUGH GEOMETRICAL TESSELLATION AND FORCES

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Tilling patterns are found in many biological structures such as insect compound eyes, columnar structures in the brain, and lobules in the liver. Among them, hexagonal tilling is dominant probably because it is superior to the other tilling patterns in terms of physical properties such as structural strength, boundary length and space filling. The Drosophila compound eye is made from ommatidial units showing regular hexagonal pattern and is an ideal model to understand the mechanism of tiling. Interestingly, it also shows tetragonal pattern in some mutant backgrounds. Here, we propose a universal mechanism of ommatidial tilling. Voronoi diagram is often used to equally divides multiple areas according to the distance from the center of each area. We found that the wildtype hexagonal pattern and mutant tetragonal pattern perfectly fit with Voronoi diagram. Incorporating the tissue-wide tension along the dorsal-ventral axis observed in vivo, the hexagonal pattern is transformed to the tetragonal pattern. How does ommatidial shape obey the geometrical Voronoi patterns? To answer this question, we focused on mutant eyes, in which the tilling pattern becomes stochastic. Surprisingly, such a stochastic ommatidial pattern also fit with Voronoi diagram except for occasional mismatching found in smaller and larger ommatidia. The growth of ommatidia, which is largely affected by the number of cells within individual ommatidia, may play critical roles. We therefore incorporated the differential growth of ommatidia into Voronoi diagram. Compared with standard Voronoi diagram, we found that weighted Voronoi diagram, in which the concentric growth rate is proportional to the ommatidial size, nicely fit with the stochastic mutant pattern. Thus, physical stretch of the eye tissue and geometrical tessellation through the concentric growth of ommatidia co-operatively determine the ommatidial tiling patterns. Physical entity that promotes the ommatidial growth will be discussed.

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ENTROPY-DRIVEN DECISION-MAKING DYNAMICS SHED LIGHT IN THE EMERGENCE OF THE PARADOX OF CHOICES

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Learning is an essential task of any living objects which sheds light on the suitability to their local environment dictates decision makers to take decisions can lead to either cooperation behaviour or antagonisitic behaviour. As the decision maker belongs to a complex microenvironment (which contains multiple decision makers), it has to take the decision where multiple options are present which often leads to a phenomenon known as paradox of choices. Now, the question is how much information of the microenvironment is too much to make the decision making at the group level? The influence of weighted individual decision-makers within the microenvironment can impact the decision-making of the central decision maker (i.e., who is making the decision)? To understand the set of questions we develop a framework based on the entropy driven decision making which can primarily answer this basic questions. Furthermore, we discovered that the paradox of choice of individual agents rely on two parameters known as interacting radius or sensing radius and sensitivity parameter. We also found that weighted individuals can make faster decision compared to the random ones. On the other hand we investigated the effect of finite memory in group level decision making to the influence of trend. At last, we incorporate the infamous Vicsek-like model as an example to demystify the origin of paradox of choices from a different facet.

FIBROUS DYSPLASIA: MATHEMATICAL MODELING APPROACH

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Fibrous dysplasia (FD) is a rare genetic disorder affecting the skeleton, characterized by the replacement of normal bone with fibrous tissue. We present a simple mathematical model of remodeling dynamics in bone affected by fibrous dysplasia, incorporating its basic known biology. Our mathematical models account for the dynamic evolution over time of several interacting populations of bone cells, including healthy bone-forming cells, mutant osteoprogenitor cells, wild-type phenocopying cells, mature bone cells, and bone-resorbing cells, averaged over a volume of bone of sufficient size. We develop an analytical study of the model and examine its basic properties. The model provides mechanistic support for various clinical observations, such as the fundamental role of the parameter measuring the flow of osteoprogenitors differentiated from mutant skeletal stem cells, which supports age-dependent normalization of FD lesions.

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CIRCULAR STRUCTURES IN HIGH DIMENSIONAL GENE EXPRESSION DATA

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Single-cell RNA sequencing (sc-RNAseq) technology enables the representation of tissues, such as a skin sample, as high-dimensional point clouds consisting of n cells within a g-dimensional gene expression space. This representation captures the "state" of each cell, facilitating the correlation of geometric and biological concepts. Circular patterns within this space are indicative of "cyclic cellular programs" (CCPs), like the cell cycle.

In practice, the analysis often involves approximately 5000 cells within a 20000-dimensional space derived from highly noisy measurements, complicating the identification of circular structures and making it a challenging problem.

In this presentation, we introduce a robust algorithm designed to detect circular patterns in lower-dimensional projections of the gene expression space by utilizing data diffusion and persistent homology. This method bridges geometric and topological features with biological concepts, associating 1-dimensional homology groups with the cyclic nature of cellular programs. Moreover, the circular coordinates of a homology group can be linked to the "intrinsic clock" of these programs.

We will conclude by discussing the potential for new biological discoveries facilitated by this approach.

MATHEMATICAL MODELS OF MMC CHEMOTHERAPY FOR NON-INVASIVE BLADDER CANCER TREATMENT PROVISIONALLY ACCEPTED

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Mitomycin-C (MMC) chemotherapy is a well-established anti-cancer treatment for non-muscle invasive bladder cancer (NMIBC). However, despite comprehensive biological research, the complete mechanism of action and an ideal regimen of MMC have not been elucidated. In this study, we present a theoretical investigation of NMIBC growth and its treatment by continuous administration of MMC chemotherapy. Using temporal ordinary differential equations (ODEs) to describe cell populations and drug molecules, we formulated the first mathematical model of tumor-immune interactions in the treatment of MMC for NMIBC, based on biological sources. Several hypothetical scenarios for NMIBC under the assumption that tumor size correlates with cell count are presented, depicting the evolution of tumors classified as small, medium, and large. These scenarios align qualitatively with clinical observations, demonstrating that cure appears up to a theoretical tumor size threshold, given specific parameters within a feasible biological range. The unique use of mole units allows to introduce a new bio-mathematical algorithm for theoretical pre-treatment assessments by determining MMC drug doses required for a cure. In this way, our approach provides initial steps toward personalized MMC chemotherapy for NMIBC patients, offering the possibility of new insights and potentially holding the key to unlocking some of its mysteries.

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SECONDARY CARBON-FIXATION IMPROVES PHOTORESPIRATION

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Photorespiration causes a significant decrease in crop yield due to mitchochondrial decarboxylation. Alternative pathways have been designed to relocate the decarboxylating step or even fix additional carbon. To improve the success of of transferring those engineeerd APs from model species to crops we must understand how they will interact with the metabolism and how the plant physiology affects their performance. Here we used multiple mathematical modelling techniques to analyse and compare existing AP designs. We show that carbon-fixing APs are the most promising candidates to replace native photorespiration in major crop species. Our results demonstrate the different metabolic mechanisms that APs employ to increase yield and which plant physiology can profit most from the respective approaches. We anticipate our results to guide the design of new APs and to help improve existing ones.

UNDERSTANDING CELL POPULATIONS SHARING INFORMATION THROUGH THE ENVIRONMENT, AS REINFORCEMENT LEARNING

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Collective migration is a widespread phenomenon observed across biological systems, from immunity to morphogenesis. Recently, much attention has been paid for cell populations that not only climb gradient of attractant emitted from targets (e.g., food) but also actively generate and degrade these attractants for sharing information about the target[1]. This information exchange through the environment is an adaptive strategy for survival in complex environment, which may be shaped optimally by evolution.

Existing mathematical models, however, often focus on macroscopic phenomena or microscopic molecular biology, lacking optimization perspectives. In this study, we address this gap by constructing a mathematical model using reinforcement learning theory[2]. Specifically, we associate the positional value, which is typically defined within an individual, with the concentration of diffusing attractant in the environment[3]. This allows us to model cell populations that actively generate and degrade diffusive attractants while climbing the gradient of attractant, as agent populations that cooperatively updating positional values under regularization constraints while climbing the gradient of positional values.

Our model is equivalent to the Keller-Segel equation in the continuous limit, suggesting that cell population might be learning in a distributed way. Furthermore, our formulation yields two possible models for learning optimal gradients: one where agents respond to logarithmic gradient and generate steeper gradient, another where agents respond to regular gradient and generate more gradual gradient. Our results demonstrate that out theoretical framework can serves as a basis for understanding how and why cell population adapt to complex environments.

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MATHEMATICAL MODEL OF CLONAL EVOLUTION PROPOSES A PERSONALISED MULTI-MODAL THERAPY FOR HIGH-RISK NEUROBLASTOMA

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Neuroblastoma is the most common extra-cranial solid tumour in children. Despite multi-modal therapy, over half of the high-risk patients will succumb. One contributing factor is the one-size-fits-all nature of multi-modal therapy. For example, during the first step (induction chemotherapy), the standard regimen (rapid COJEC) administers fixed doses of chemotherapeutic agents in eight two-week cycles. Perhaps because of differences in resistance, this standard regimen results in highly heterogeneous outcomes in different tumours. In this study, we formulated a mathematical model comprising ordinary differential equations. The equations describe the clonal evolution within a neuroblastoma tumour being treated with vincristine and cyclophosphamide, which are used in the rapid COJEC regimen, including genetically conferred and phenotypic drug resistance. The equations also describe the agents' pharmacokinetics. We devised an optimisation algorithm to find the best chemotherapy schedules for tumours with different pre-treatment clonal compositions. The optimised chemotherapy schedules exploit the cytotoxic difference between the two drugs and intra-tumoural clonal competition to shrink the tumours as much as possible during induction chemotherapy and before surgical removal. They indicate that induction chemotherapy can be improved by finding and using personalised schedules. More broadly, we propose that the overall multi-modal therapy can be enhanced by employing targeted therapies against the mutations and oncogenic pathways enriched and activated by the chemotherapeutic agents. To translate the proposed personalised multi-modal therapy into clinical use, patient-specific model calibration and treatment optimisation are necessary. This entails a decision support system informed by emerging medical technologies such as multi-region sequencing and liquid biopsies. The results and tools presented in this paper could be the foundation of this decision support system.

MACHINE LEARNING-BASED DETECTION OF POTENTIAL BIOMARKER FOR IDENTIFICATION OF PSEUDO-STAGE OF HTLV-1-ASSOCIATED MYELOPATHY (HAM) USING ANTI-

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This study leverages anomaly detection and machine learning classification to identify and categorize individuals at an intermediate stage of developing HAM/TSP. Initially, we employed an unsupervised anomaly detection method to a non-time series dataset of antibody titers to HTLV-1 antigens and Pro-viral load (PVL) from asymptomatic HTLV-1 Carriers (n=264). This approach was aimed at identifying anomalous data points supposedly indicative of an intermediary phase, which we termed 'pseudo-stage', preceding the onset of HTLV-1-associated diseases. Through comprehensive feature analysis, Gag p24 was identified as the principal biomarker signaling the transition from the asymptomatic Carrier stage toward the pseudo-stage. Subsequently, we developed and validated classifier models capable of distinguishing between three clinical conditions: Carrier, ATL, and HAM, and used the best model to predict the outcome from the anomaly carrier samples as unseen data. The majority of these samples were predicted as HAM which indicates a progressive disease status. Further feature analysis within this classification framework highlighted Tax as a significant marker for the prediction of HAM. Our analysis reveals a marked diversity in immune responses suggesting a sequential biomarker evolution where elevated Gag p24 levels initially mark the progression to an intermediate pseudo-stage, followed by the emergence of Tax as a critical determinant in developing HAM/TSP. This study underscores the potential of utilizing Gag p24 and Tax as sequential biomarkers for early detection and classification of high-risk Carriers, offering new insights into the immunopathological changes occurring from the intermediate pseudo-stage to the full manifestation of HAM/TSP.

MODEL OF TUMOR GROWTH IN GLIOMAS. SURVIVAL ANALYSIS IN VIRTUAL PATIENTS.

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Cancer is the second cause of death in the world and this makes it a priority to investigate the disease and treatments that combat it. This research proposes a system of differential equations that describes the growth of a highly malignant glioma under the treatment of radiotherapy and an immunotherapy called Nimotuzumab. This immunotherapy was developed by the Center for Molecular Immunology in Havana, Cuba and is the first time that its effect has been taken into account in a mathematical model of growth. Despite having few measurements over time from real patients, it was possible to observe that the model described a logical dynamic not far from reality.

This model was later used to simulate virtual glioma patients with the established scheme and other proposed ones that use fewer doses of Nimotuzumab. A variable of interest in these patients was their survival time, information that was collected in a database and used to calculate the sample size necessary to carry out a virtual clinical trial, under the hypothesis of non-inferiority of the schemes proposed with respect to the established one. With the help of the Kaplan-Meier Estimator and Cox Regression, it was shown that one of the proposed schemes had the same effect on the survival time of the patients as the established one, which is a good result because this new scheme not only is it beneficial to patients by avoiding administrations so close together, it could also generate significant savings in treatment costs or allow the use of additional doses in other patients.

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CONFORMATIONAL DYNAMICS OF GALECTIN-3 BASED ON THE MARTINI 3 MODEL

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Biomolecular condensates (BCs), comprised mainly of intrinsically disordered proteins, form through liquid–liquid phase separation within biological cells. Despite considerable research on BCs in the cytosol and nucleus, their behavior at cellular membranes remains largely unexplored. Galectin-3, a mixed-folded protein consisting of an intrinsically disordered N-terminal domain (NTD) and a carbohydrate recognition domain (CRD), plays pivotal roles in various biological processes such as immune responses, cell migration, and signaling. It has been demonstrated that galectin-3 interacts with glycosphingolipids on the cell membrane, facilitating clathrin-independent endocytosis [1]. Using dissipative particle dynamics simulations, we explore how polymer models resembling galectin-3 sense and respond to membrane curvature. Our findings suggest a generic mechanism by which BCs sense membrane curvature, potentially influencing such cellular processes as endocytosis [2]. To elucidate the conformational dynamics of galectin-3, we conduct molecular dynamic simulations using the Martini 3 force field . Following the method introduced by Thomasen et al. [3] for rescaling protein-water interactions, we generate a conformational ensemble consistent with data from small angle X-ray scattering experiments . Our simulations reveal large-scale fluctuations between compact and extended conformations of galectin-3, with aromatic residues within the NTD forming most frequent contacts.

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PATTERNS IN THE KELLER-SEGEL SYSTEM WITH DENSITY CUT-OFF

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The Patlak-Keller-Segel system with logistic sensitivity has been widely advocated as a model which avoids over-crowding and generates complex patterns. In this presentation, we will focus on the general case of a nonlinear diffusion of porous medium type with an exponent. We will show that the pattern formation ability of such a system depends highly on exponent and three regimes occur for linear diffusion and non-linear diffusion. Within these regimes the sensitivity also plays a crucial role as well as the conserved total mass. We will focus specifically on the conditions for long term convergence to the constant solution, uniqueness of the steady state and on the contrary, existence of increasing steady solutions in dimension one. In opposition to the case with linear diffusion, is that solutions can vanish locally with non-linear diffusion.

ANALYSIS OF A DETAILED MULTI-STAGE MODEL OF STOCHASTIC GENE EXPRESSION USING QUEUEING THEORY AND MODEL REDUCTION

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We introduce a biologically detailed, stochastic model of gene expression describing the multiple rate-limiting steps of transcription, nuclear pre-mRNA processing, nuclear mRNA export, cytoplasmic mRNA degradation and translation of mRNA into protein. The processes in sub-cellular compartments are described by an arbitrary number of processing stages, thus accounting for a significantly finer molecular description of gene expression than conventional models such as the telegraph, two-stage and three-stage models of gene expression. We use two distinct tools, queueing theory and model reduction using the slow-scale linear-noise approximation, to derive exact or approximate analytic expressions for the moments or distributions of nuclear mRNA, cytoplasmic mRNA and protein fluctuations, as well as lower bounds for their Fano factors in steady-state conditions. We use these to study the phase diagram of the stochastic model; in particular we derive parametric conditions determining three types of transitions in the properties of mRNA fluctuations: from sub-Poissonian to super-Poissonian noise, from high noise in the nucleus to high noise in the cytoplasm, and from a monotonic increase to a monotonic decrease of the Fano factor with the number of processing stages. In contrast, protein fluctuations are always super-Poissonian and show weak dependence on the number of mRNA processing stages. Our results delineate the region of parameter space where conventional models give qualitatively incorrect results and provide insight into how the number of processing stages, e.g. the number of rate-limiting steps in initiation, splicing and mRNA degradation, shape stochastic gene expression by modulation of molecular memory.

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STATISTICAL MODELING AND PHYLOGENETIC ANALYSIS OF SARS-COV-2 IN MALAWI

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The novel SARS-CoV-2 Coronavirus that causes COVID-19 was first identified in a person in Wuhan city, China in December 2019. The virus spread to all continents in less than three months. Malawi had its first case on 2 April 2020. This contribution will present results from a study modelling SARS-CoV-2 using statistical methods and analysing the evolution of the virus in Malawi from 2 April 2020 to 19 October 2022. Case and genome data of SARS-CoV-2 for Malawi were open source and obtained from Our World in Data and GISAID websites, respectively.

Generalised Additive Models (GAM) were fit to case and mortality data to describe the trends, growth rate and doubling time of SARS-CoV-2, while IQTree, TreeTime and interactive Tree of Life tools were used to perform the phylogenetic analysis.

Five major variants of SARS-CoV-2 were identified: Alpha, Beta, Delta, Omicron and Other, with Other representing the variants circulating before the emergence of the Variants of Concern (VoCs). Malawi experienced four waves of SARS-CoV-2 with each wave dominated by each of Other, Beta, Delta and Omicron. Very few Alpha sequences were found in Malawi. Cases and deaths escalated when each new variant emerged in January, June, July and December 2021. Delta and Omicron variants in Malawi had the time of most recent common ancestor much earlier in calendar compared to South Africa and the UK. Additionally, the infection was more severe in Malawi when compared to some African countries but less severe when compared to high-income countries and; had a general decreasing trend of infectiousness.

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NATURAL DEATH RATE DRIVES STAR GRAPHS FROM AMPLIFIERS TO SUPPRESSORS OF NATURAL SELECTION

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Evolutionary graph theory (EGT) considers evolutionary dynamics in a structured population that is represented by a graph. Fixation probability is a measure of probability that a mutation takes over the resident population. One of the major questions EGT tries to answer is how the graph structure impacts the fixation probability. It has been found that certain graphs can act as amplifiers or suppressors of selection. However, the type of update rule used in the model can impact this result. For example, the star graph is an amplifier for birth-death with fitness on birth (Bd) dynamics and is a suppressor for death-birth with fitness on birth (dB) dynamics.

Typically, EGT has focused on discrete time models, which can be hard to link with realistic population dynamics. Recently, these discrete time models have been generalized to a continuous time Markov-process model based on eco-evolutionary dynamics, where the results for dB and Bd dynamics can be recreated by suppressing the ecological dynamics.

This work shows that within this continuous time framework, there exists a continuous transition from Bd to dB results. Therefore, the interplay between the underlying biological parameters of birth rate, death rate, and competition, will drive the qualitative shift from amplifier (under Bd) to suppressor (under dB). Using the star graph as an example, we prove that the transition from Bd to dB depends on the magnitude of the natural death rate. By increasing the natural death rate of individuals, population structures that typically amplify selection under Bd dynamics can be driven to suppressing fixation. Exploring the fundamental drivers behind this qualitative shift will provide further insights into whether population structures will amplify or suppress selection under realistic population dynamics.

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CLASSIFYING AND CHARACTERIZING RANDOM WALKS FROM FLUORESCENCE CORRELATION SPECTROSCOPY WITH MACHINE LEARNING

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The motion of molecules and multi-molecular particles in live cells has been observed to deviate from standard Brownian motion, which is called "anomalous diffusion". To study this phenomenon in live cells, two major types of experimental approaches are used: those based on the tracking of individual markers, single-particle tracking (SPT) and those based on the auto-correlation of a handful of fluorescent markers fluorescence correlation spectroscopy (FCS). Each method has its own limitations and associated temporal and spatial scales.

With the classical analysis methodology, FCS cannot consider molecular motions for which no analytical expression of the auto-correlation function is known, including anomalous continuous - time random walks (CTRW). Additionally, the whole acquisition sequence of the classical FCS methodology takes several tens of minutes.

A new analysis approach is proposed to address these limitations. This approach associates each individual FCS recording with a vector feature based on an estimator of the auto-correlation function and uses machine learning to infer the underlying model of motion and estimate the values of the motion parameters. Using simulated recordings, it is shown that this approach enables FCS to distinguish between a range of standard and anomalous random motions, including CTRW. The approach exhibits comparable performance to the best-in-class algorithms for SPT and can be used with a range of FCS setup parameters.

The new method allows FCS to monitor rapid changes in the motion parameters and can be applied on individual recordings of short duration. When applied to in vitro experimental FCS recordings of calibrated fluorescent beads in increasing concentrations of glycerol in water, the results confirm previous reports of the emergence of anomalous diffusion. The results also show that the anomalous properties of the bead motion progressively transition from transitory to permanent as the glycerol concentration increases.

INFECTION MODELING IN A MULTISCALE MATHEMATICAL SYSTEM

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We propose a hybrid partial differential equation - agent-based (PDE-ABM) model to describe the spatio-temporal infection dynamics in a cell population. Concentration of virus or bacteria is considered as a continuous variable, while changes in the states of cells are represented by a stochastic agent-based model. The two subsystems are naturally intertwined.

Our corresponding in silico results are presented for multiple scenarios. From exploring SARS-CoV-2 infection dynamics and investigating the antiviral effect of Paxlovid to modeling the bacterial infection of joints, the proposed hybrid model can help us gain insight into treatment optimization.

THE BURR DISTRIBUTION AS A MODEL FOR THE DELAY BETWEEN KEY EVENTS IN AN INDIVIDUAL'S INFECTION HISTORY

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Understanding the temporal relationship between key events in an individual's infection history is crucial for disease control. Delay data between events, such as infection and symptom onset times, is doubly censored because the exact time at which these key events occur are generally unknown. Current mathematical models for delay distributions rely solely on heuristic justifications for their applicability. Here, we derive a new model for delay distributions, specifically for incubation periods, motivated by bacterial-growth dynamics that lead to the Burr family of distributions being a valid modelling choice. We also incorporate methods within these models to account for the doubly censored data. Our approach provides biological justification in the derivation of our delay distribution model, the results of fitting to data highlighting the superiority of the Burr model compared to currently used models in the literature. Our results indicate that the derived Burr distribution is 13 times more likely to be a preferable model to incubation period data than currently used methods. Further, we show that incorporating methods for handling the censoring issue resulted in underlying continuous incubation period model mean being reduced by a whole day compared to current understanding based from previous modelling techniques in the literature.

MATHEMATICS AS A BASIS FOR THE DETECTION OF SUPERATIGEN SEQUENCES.

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Biomathematics, in particular Mathematical Immunology, is a field of research that allows the analysis of a wide number of genomic and amino acid sequences, as well as the growing number of three-dimensional (3D) structures of proteins [1] and other available macromolecules. Structure-Function Prediction (SFP) of proteins, together with the combination of Multiple Sequence Alignments (MSAs) and genetic analyses, facilitate making predictions about functional aspects of proteins. In this way, specific sites for a specific group of sequences, also called SDPs (specificity determining positions) could be identified (in silico). In this study, I analyze a mathematical immunology model on a group of protein toxins from Streptococus pyogenes and Staphylococcus aureus called Superantigens (SAgs) in order to recognize, first, if an amino acid sequence is a SAgs and, second, identify specific sites interaction with the MHC (major histocompatibility complex).

LARGE DEVIATIONS IN A GENE EXPRESSION MODEL WITH FEEDBACK IN BURST SIZE

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Synthesis of gene products in bursts of multiple molecule copies is an important source of gene expression variability. Bursty gene expression can be modelled by a Markov drift-jump process that combines random bursts with deterministic decay. We focus on characterising large deviations of the steady state process in the regime of frequent bursts. Similarly as in diffusion processes, large deviations can occur as a cumulative effect of many bursts. In this case, the stationary probability distribution can be approximated using a routine application of the Wentzel–Kramers–Brillouin (WKB) method. However, if the model includes negative feedback in burst size, then large deviations can result from a single big jump (burst). In this case, the routine WKB solution needs to be replaced in the tail of the distribution by an envelope of big jump log-probabilities. Notably, the modified tail is heavier than predicted by the routine application of the WKB scheme.

STOCHASTIC MODELLING OF LINEAGE CORRELATIONS IN GLIOBLASTOMA CELLS TO CAPTURE NON-GENETIC HETEROGENEITY

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Glioblastoma is one of the most aggressive and difficult to treat cancers. One obstacle to developing successful treatments is the substantial interpatient and intratumour heterogeneity. This variability in treatment response even occurs in genetically identical cells and could be due to inherent randomness in gene expression. However, non-intuitive correlation structures in the division and death dynamics of genealogically related cells imply an unrecognised deterministic process. We developed a mathematical modelling framework to distinguish between multiple different hypotheses governing heterogeneity in cell proliferation and death following radiotherapy.

We use live-cell imaging data of different glioblastoma patient-derived cell lines with stably expressed H2B reporters to identify and track their nuclei. We constructed an image analysis pipeline to automatically extract cell fates and construct lineage trees from the microscopy data. We developed multiple mathematical models representing different hypotheses for the inheritance mechanism of cell fate propensities, including single-factor inheritance from mother cells and circadian rhythm-modulated division and death rates. The models are formulated within the Bayesian framework to capture the high levels of stochasticity and allow for a probabilistic interpretation of the results. Model parameters describing proliferation and death rates as well as the correlation structure within a lineage are inferred statistically and a model comparison is carried out to quantify the goodness of fit of the hypotheses for several datasets. Once complete, our parameterised mathematical models could be used to simulate the responses of the cancer cells to different treatment strategies, such as chronotherapy or novel drug-radiation combinations.

BIOLOGICALLY MEANINGFUL REGULATORY LOGIC ENHANCES THE CONVERGENCE RATE IN BOOLEAN NETWORKS AND BUSHINESS OF THEIR STATE TRANSITION GRAPH

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Boolean models of gene regulatory networks (GRNs) have gained widespread traction as they can easily recapitulate cellular phenotypes via their attractor states. Their overall dynamics are embodied in a state transition graph (STG). Indeed, two Boolean networks (BNs) with the same network structure and attractors can have drastically different STGs depending on the type of Boolean functions (BFs) employed. Our objective here is to systematically delineate the effects of different classes of BFs on the structural features of the STG of reconstructed Boolean GRNs while keeping network structure and biological attractors fixed, and explore the characteristics of BFs that drive those features. Using 10 reconstructed Boolean GRNs, we generate ensembles that differ in BFs and compute from their STGs the dynamics' rate of contraction or 'bushiness' and rate of 'convergence', quantified with measures inspired from cellular automata (CA) that are based on the garden-of-Eden (GoE) states. We find that biologically meaningful BFs lead to higher STG 'bushiness' and 'convergence' than random ones. Obtaining such 'global' measures gets computationally expensive with larger network sizes, stressing the need for feasible proxies. So we adapt Wuensche's Z-parameter in CA to BFs in BNs and provide 4 natural variants, which along with the average sensitivity of BFs, computed at the network level, comprise our descriptors of local dynamics and we find some of them to be good proxies for bushiness. Finally, we provide an excellent proxy for the 'convergence' based on computing transient lengths originating at random states rather than GoE states.

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MINGLE: A NEW TOOL FOR ADVANCING MULTI-OMICS NETWORK INTEGRATION AND VISUALIZATION

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Discovery key relations among molecular entities is extremely important in clinical applications. Network inference methods based on omics data represent a powerful tool to achieve this goal, providing crucial insights for improving disease understanding [1]. However, when multi-omics layers are considered, the interpretation of such networks might be challenging [2]. To address this problem, we present MINGLE (Multi-omics Integrated Network for GraphicaL Exploration), a novel methodology designed to merge distinct multi-omics information into a single network, enabling the identification of underlying relations through an innovative integrated visualization. MINGLE is built into a network estimation framework, developed to elucidate glioma brain cancer heterogeneity based on RNA sequencing and DNA methylation data. The presented study allowed the identification of relations from a multi-omics perspective, which might be potentially involved in glioma-type-specific regulation processes.

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MATHEMATICAL MODELING OF THE IIS, TORC1 SIGNALING PATHWAYS AND MICRORNAS IN CAENORHABDITIS ELEGANS, EXPOSED TO HIGH-GLUCOSE DIETS OR FASTING

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We inferred a network of the Insulin/IGF1 (IIS) and TORC signalling pathways, that included microRNAs that regulate the genes of these pathways in Caenorhabditis elegans. We selected theses genes because they are the ones who change their expression in high-glucose diets of fasting, and also involved in the control of longevity and metabolism of lipids. We analyzed our network through boolean networks, a type of discrete math model. We obtained six fixed-point attractors. Five of them faithfully reproduced the data found in the literature. Two of them were akin to the fasting condition with a high expression of pro-longevity genes, demonstrating the known positive effect of fasting on longevity. Two of the attractors were observed that were similar to control diet. Another attractor was associated to high-glucose diets that showed a high proportion of expression of anti-longevity genes, concordant with the negative effect that high-glucose diets have on longevity. Interestingly, we obtained one attractor that has not been observed experimentally, which represents a prediction of our model. This attractor was in high-glucose diet with genes prolongevity, suggests a positive effect this diet. Furthermore, our model reproduced very well simulations Knock-out, which were consistent with experimental data. Finally, our model replicated similar data to those reported in C. elegans when exposed to metformin.

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ARTIFICIAL INTELLIGENCE ADVANCEMENTS FOR THE DETECTION OF ACUTE LYMPHOBLASTIC LEUKEMIA RELAPSE

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In the last decade, the use of artificial intelligence (AI) techniques has experienced a significant surge across various fields, fundamentally transforming how we analyze and understand complex data. In the healthcare sector, AI promises to revolutionize medical diagnosis, therapeutic efficacy and patient outcomes.

In the context of hematological diseases such as acute lymphoblastic leukemia (ALL), AI tools offer new perspectives for exploring the vast amount of data generated by flow cytometry techniques. The combination of AI algorithms with clinical data opens the door to a better understanding of the underlying disease mechanisms [1,2]. These include the identification of specific biomarkers for more precise and personalized therapeutic intervention.

This study is focused on analyzing samples from 188 patients, with approximately 20% of them experiencing a relapse in ALL. By using advanced machine learning techniques, such as classification and regression algorithms, the aim was to distinguish between patients with and without relapse, in order to develop more accurate and robust predictive models. Cross-validation and sample rebalancing strategies were implemented to ensure the reliability of the results.

The findings of this study highlight the transformative potential of artificial intelligence in the field of hematology, paving the way for more personalized and efficient healthcare for patients with ALL and other hematological diseases.

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INVESTIGATING A SPATIALLY AND TEMPORALLY HETEROGENEOUS MODEL OF CYCLIC HYPOXIA AND THE CELL CYCLE WITHIN SOLID TUMOURS.

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Hypoxia refers to physiologically low levels of oxygen in tissue and is present within most solid tumours. There are two main types of hypoxia, constant/chronic and acute/cyclic, and both have been shown to lead to poor patient outcomes. However, it is difficult to compare experimental studies that focus on cyclic hypoxia due to the array of different conditions used to create the "cycles". Mathematical models represent a promising avenue for studying such complex oxygen dynamics. The mitotic cell cycle controls DNA replication and cell division, and is regulated in part by environmental oxygen levels. Furthermore, the efficacy of cancer treatments such as radiotherapy depend on both oxygen levels and a cell's position within the cell cycle, with increased resistance found for hypoxic cells and during DNA replication. Existing mathematical models of these interactions have considered spatially homogenous environments, with temporally fluctuating oxygen levels. As such, they cannot capture the spatial heterogeneity seen in vivo. To this end, we have reformulated and extended a previous model to account for spatial heterogeneity. Specifically, we have derived a system of partial differential equations (PDEs) which structures cells by the position within the cell cycle and allows for spatial heterogeneity of oxygen via diffusion and cellular consumption. Initial work has focused on studying the model in spatially homogeneous, physiological levels of oxygen (i.e., normoxia), and comparing these results to those from an existing, compartment-based ordinary differential equation (ODE) model. The relative simplicity of the PDE model allows analytical solutions to be constructed, and we find that the PDE exhibits qualitatively different behaviour to the ODE system, suggesting that the compartment-based approach may be invalid in certain cases. In further work, we have used numerical methods, such as finite volume and finite element methods, to analyse the full PDE system.

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ACCESSION-SPECIFIC LARGE-SCALE KINETIC MODEL OF C4 PHOTOSYNTHESIS

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Photosynthesis is the workhorse for growth of all crops and is one of the key targets for improving agricultural productivity. The photosynthetic efficiency differs both between and within species, and photosynthetic responses have been intensively measured under varying CO2 concentrations and light intensities (represented by A-Ci and A-Q curves). While many published kinetic models of photosynthesis were used to simulate photosynthetic response and to propose different hypotheses, their kinetic parameters were collected from literature or estimated in different species. Yet, the differences in kinetic parameters of enzymes involved in photosynthesis between different genotypes are not fully explored. Here, we make use of a detailed kinetic model to simulate the changes of metabolites and fluxes over time with the aim of mimicking the diversity of observed A-Ci or A-Q curves across different genotypes and species. To address this problem, we parameterized a kinetic model for C4 photosynthesis [1] allowing accurate simulation of A-Ci or A-Q curves measured for 70 inbred lines from a maize MAGIC population [2]. The genotype-specific kinetic parameters are then used to train a machine learning model that can predict the parameter values for accessions for which only genomic data are available as input. As a result, our findings facilitate the simulation of photosynthetic profiles for a large number of maize accessions, which can be then ranked according to their predicted photosynthetic efficiency.

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AGENT-BASED MODELLING OF CELL DIFFERENTIATION PATTERNS IN MOUSE BLASTOCYSTS

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Early embryonic development from zygote to blastocyst is a highly dynamic, self-organised process in which stem cells undergo successive cell fate decisions and form a complex structure. Local patterns in the early and mid blastocyst stage resolve into global patterns in the late stage of the blastocyst [1]. A first modelling approach, based on cell division and signalling showed that the spatial cell fate patterns arising in the early and mid stage, are compatible with signalling beyond the nearest neighbours [2,3]. As a next step, we aim at expanding our existing mathematical, agent-based model to incorporate the late stage. The resulting model consists of cell division, cell death, physical interactions, transcription and signalling between the cells. The model allows to systematically investigate the influence of these mechanisms and their relative timing with respect to the formation of the global pattern in the late blastocyst stage. Due to its modular structure, we expect the model to be applicable to cell differentiation in other 2D or 3D cellular systems.

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EXPERIMENTALLY-DRIVEN MATHEMATICAL MODEL TO UNDERSTAND THE EFFECTS OF MATRIX DEPRIVATION IN BREAST CANCER METASTASIS

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Normal epithelial cells receive proper signals for growth and survival from their attachment to the underlying extracellular matrix (ECM). They perceive detachment from the ECM as a stress and die. This cell death triggered by matrix detachment is known as anoikis. However, cancer cells are anoikis-resistant. Under normal (adherent) growth conditions, the serine-threonine protein kinase Akt plays a major role in cell proliferation and protein synthesis, maintaining an anabolic state in the cancer cell. In contrast, we showed that the stress due to matrix deprivation is sensed by yet another serine-threonine kinase AMP-activated protein kinase (AMPK) in response to a spike in intracellular calcium. We also showed the existence of an AMPK-Akt double-negative feedback loop in breast cancer cells that regulates their adaptation to matrix deprivation. We illustrated a metabolic switching from an anabolic to a catabolic state upon matrix-deprivation, which aids cancer cell stress-survival. In this study, we utilized these experimental data and developed a mathematical model to capture the pathophysiology of matrix-deprived state in breast cancer cells. To do so, we used the mathematical framework of an insulin-glucagon hormone signaling network that maintains the balance between anabolism and catabolism to maintain metabolic homeostasis. Using this model, we identified several proteins which are perturbed upon matrix deprivation in addition to AMPK and Akt. These include IRS, PI3K, GLUT1, IP3, DAG cAMP, PKA and PDE3. Molecular perturbations revealed that several feedback/crosstalks like PKC to IRS, S6K1 to IRS, cAMP to PKA, AMPK to Akt and DAG to PKC are crucial in maintaining the metabolic switching from an anabolic to catabolic state upon matrix deprivation. Upon their removal, metabolic switching is curbed. Thus, we have developed a unique mathematical framework to simulate the molecular interplay with metabolic adaptations critical for cancer metastasis.

OPTIMAL CONTROL OF STOCHASTIC REACTION NETWORKS WITH KL CONTROL COST

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Optimal control problems for the population of interacting particles arise in various fields, including pandemic management, species conservation, cancer therapy, and chemical engineering. When the population size is small, the time evolution of the particle numbers is inherently noisy and modeled by stochastic reaction networks, a class of jump processes on the space of particle number distributions. However, compared to deterministic and other stochastic models, optimal control problems for stochastic reaction networks have not been studied well. This is partly due to the absence of a mathematically and computationally nice framework, such as the Linear-Quadratic-Gaussian (LQG) setting for diffusion processes. Without such a framework, one has to solve a large system of nonlinear (differential) equations, known as the Hamilton–Jacobi–Bellman (HJB) equation, to calculate the optimal solution. In this study, we propose a mathematically and computationally nice framework for stochastic optimal control of reaction networks. By utilizing the Kullback–Leibler (KL) divergence as a control cost, the HJB equations can be linearized. This approach allows us to efficiently obtain the optimal solution, which shares a similar mathematical structure with previously discovered linearly solvable optimal control problems [1,2,3]. We apply this framework to the control of interacting random walkers, birth-death processes, and stochastic SIR models, presenting numerical solutions, and even analytical solutions for some problems.

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GEOMETRY OF IMMUNOSUPPRESSION IN CAR-T CELL TREATMENT: INSIGHTS FROM MATHEMATICAL MODELING

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Immunotherapy has seen significant advancements through chimeric antigen receptor T cell (CAR) therapy, wherein a patient's T lymphocytes are genetically engineered to recognize tumor-specific antigens, enhancing tumor elimination efficiency. In recent years, CAR-T cell immunotherapy, acclaimed for its success in hematological malignancies, has emerged as a promising treatment for solid tumors, driving ongoing research. Theoretical models are pivotal in simplifying intricate immune system interactions, aiding in understanding and predicting behavior, particularly in solid tumors. This study evaluates the potential of cellular automata as a modeling tool for analyzing dynamic interactions between tumor cells and CAR-T cells. The primary aim is to deepen our understanding of treatment effects by exploring scenarios based on initial tumor cell and CAR-T cell quantities. A notable finding is the significant impact of tumor geometry on treatment efficacy, with distinct responses observed between tumors exhibiting block-like arrangements and those with dispersed cell distributions.

TOWARDS A GENERIC TICK LIFE CYCLE MODEL

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The aim of our work is to develop a conceptual generic agent-based model to formalize the interaction of vector and host given climate change. The model consists in creating a hypothetical example of a vector-host system. It simulates the vector's life cycle while considering interactions with hosts and the temperature. It is presented following the ODD protocol and based on parameters and processes to conceptualize the vector-host complexity. It could accommodate a broad spectrum of vector species and different biogeographic regions. Our model can be extended to more ecologically complex systems with multiple species and real-world landscape complexity to test different host- and/or vector-targeted control strategies and identify practical approaches to managing vector population and movement patterns.

SPATIAL-TEMPORAL HETEROGENEITIES IN ASSOCIATIONS BETWEEN HUMAN MOBILITY AND COVID-19 TRANSMISSION

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Human mobility significantly influences the dynamics of COVID-19 transmission. The effectiveness of mobility-related intervention measures, however, has exhibited considerable variation across different regions and time periods. In the initial stages of the pandemic, with pharmaceutical interventions still under development, many countries resorted to intensive non-pharmaceutical strategies, such as lockdown policies and contact tracing. However, as the pandemic progressed and vaccination-led herd immunity began to take effect, reliance on mobility restrictions waned, diminishing the impact of human mobility on COVID-19 transmission dynamics.

This study aims to explore the spatial-temporal heterogeneity of the COVID-19 epidemic. By analyzing provincial-level data on human mobility and COVID-19 case counts, we investigate the varying effectiveness of mobility restrictions in controlling the virus's spread across different regions. This analysis will shed light on the complex interplay between human movement patterns and the transmission of infectious diseases, providing valuable insights for shaping future public health policies.

ADDRESSING BIAS IN EPIDEMIOLOGICAL PARAMETER ESTIMATION: A BAYESIAN APPROACH WITH REALISTIC DISTRIBUTIONS OF LATENT AND INFECTIOUS PERIODS

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Infectious diseases are transmitted through the transfer of pathogens between individuals. Typically, following exposure, a latent period occurs before an individual becomes infectious, and subsequently, they lose infectiousness after a certain period. The emergence and disappearance of pathogens within an individual are time-dependent, meaning the likelihood of becoming infectious or recovering changes over time since exposure or the onset of infectiousness. This leads to non-Markovian dynamics, presenting significant challenges in modeling and inference. Traditional models often rely on an unrealistic assumption of history-independent transitions, where the probability of transition remains constant irrespective of the time elapsed since exposure or onset of infectiousness. This assumption implies that the latent and infectious periods follow an exponential distribution. However, our research has identified that this prevalent assumption introduces substantial biases in estimating key epidemiological parameters, such as the reproduction number (R), which are vital for devising intervention policies. To mitigate this bias, we have developed a Bayesian inference method that employs realistic gamma distributions for latent and infectious periods. Our approach not only estimates R and the distribution of the infectious period with high accuracy and precision from confirmed case data alone, differing significantly from conventional methods, but it also sheds light on the evolution of the infectious period distribution during the COVID-19 pandemic. This insight is crucial for understanding the changing effectiveness of intervention strategies over time.

A THOUGHT EXPERIMENT ON THREE METRICS OF MATRIX POPULATION MODELS

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Matrix population models have been often employed as an effective tool to quantify the properties of population dynamics of plants and animals. The population growth rate, stable stage distribution and reproductive value are three major metrics of the model and can be obtained using the knowledge of linear algebra. That is, they are equivalent to the dominant eigenvalue of the projection matrix in the model, right and left eigenvectors corresponding to the dominant eigenvalue, respectively [1]. Using a thought experiment, we reconsider the meaning of three metrics, based on two simple assumptions. Suppose that we don't know the concept of eigenvalue as well as eigenvalue equation. Therefore, we don't know how to obtain eigenvalues and eigenvectors. We assume that the dynamics of matrix population models shows a stable behavior, i.e. when the time elapsed sufficiently, the number of individuals at each developmental stage increases at a constant rate (Assumption 1; population growth rate) and the proportion of individuals at each stage (Assumption 2; stable stage distribution) is kept constant. Under these two assumptions, we obtain the following results: (1) Based on a new metric named inter-stage flow, we have a conservation law, that is, the sum of all elements in inter-stage flow matrix is equal to the population growth rate. (2) Based on the definition of reproductive value in stage-structured models analogous to Fisher's reproductive value in age-structured models, we can prove the reproductive value in stage-structured models is equivalent to the left eigenvector of projection matrix.

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MODELLING TRIPARTITE MICROBIAL POPULATION DYNAMICS

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Mathematical models can be used to systematically unravel the intricacies of coexistence and competition dynamics among the members of microbial colonies over time. The study extensively explores the metabolic interactions occurring over time within the heterotrophic members of microbial communities by emphasizing the co-cultivation of photoautotrophic and heterotrophic partners within the community structure. The primary focus of this work is to analyze the impacts of selected three metabolic strategies- Public metabolizer, Private metabolizer, and Cheater on the consortium dynamics, composition, and stability. We expand the nonlinear Lotka-Volterra framework to an extra dimension by incorporating a model of a three-strain microbial community and it serves as the framework for our investigation.

A critical aspect of our inquiry involves examining the stability condition of our proposed nonlinear differential model. We incorporate i) Jacobi Stability ii) Manifold Theory iii) Liapunav Function to the study of equilibrium points of the system in terms of their stability properties. This analytical approach enables us to understand the stability and instability conditions of cooperation and competition which indicate the general rules for the survival and extinction of the members of our designed synthetic cross-kingdom community connected through nutrient exchange.

We anticipate that a better knowledge of the activities of microbial communities will result from our study. This work provides valuable insights into the ecological dynamics of microbial systems and offers a foundation for further investigations into the impact of cheating behavior and light manipulation of phototrophs on communities' stability and resilience. The anticipated outcomes may influence various domains, including environmental management, ecosystem engineering, and applications in biotechnology, by shaping creative approaches based on the study's discoveries.

TURNOVER SHAPES EVOLUTION OF BIRTH AND DEATH RATES

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A truly predictive evolutionary theory must be derived self-consistently from the underlying stochastic population dynamics, where the environment and ecology are not treated merely as confounders and mediators of evolutionary dynamics. By explicitly decomposing fitness to its birth and death components as well as accounting for how evolution and ecology respectively might affect them, we show how a fundamental asymmetry in evolutionary innovation towards reproduction and survival emerges. First, we show how the demographic turnover rate shapes the distribution of evolutionary trajectories causing a systematic turnover bias in the mutant substitution dynamics. This causes the observed mean trajectory to deviate from the deterministic selection gradient in favour of less volatile low-turnover strategies. Then we provide theory for predicting how organismal growth strategies evolve in response to different population regulation mechanisms and show how the resulting life-history evolution has a clear direction where the pace of life becomes either slower or faster depending on the ecological context and mutational supply. Overall, our results highlight the importance of demographic turnover in evolution and underline the perils of quantifying fitness with a single parameter.

MODELING THE INTERACTIVE EFFECTS OF BACKYARD BIRD FEEDING, PREDATION, AND INFECTION IN WILD BIRD POPULATIONS

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Human activities such as agriculture, landfills, and recreational feeding provide reliable food sources for wildlife that profoundly influence wildlife populations and species interactions and can promote the transmission of infectious diseases among wildlife, domestic animals, and humans. Millions of households partake in backyard bird feeding worldwide, but direct nutritional benefits to birds could be offset by increased risk of predation or disease outbreaks. Given pervasive declines in bird populations, it is crucial to understand the net effects of feeding that account for both the direct effects of supplemental food and the indirect effects of altered species interactions. We developed a differential equation model to simulate bird-pathogen interactions at bird feeders in the presence of predators, where food subsidy influences parameters describing host fitness, pathogen transmission, and predation risk. First, we calculated the pathogen's basic reproduction number under food subsidy. We found that predators are most likely to prevent outbreaks when food subsidies decrease feeder bird susceptibility to infection or when infected birds are preferentially predated and are least likely to prevent outbreaks when subsidies increase bird abundance at feeders. Next, we solved the model numerically to calculate cumulative bird mortality over a winter season. We found that low virulence-high transmission pathogens increased mortality the most when infected birds were selectively predated, while high virulence-low transmission pathogens decreased overall bird mortality. These findings highlight the importance of understanding community interactions around food subsidies and could inform guidelines for the management of wildlife feeding in the presence of predators and pathogens.

FLEXIBLE NETS TO MODEL UNCERTAIN BIOMASS COMPOSITION IN BIOLOGICAL SYSTEMS

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Genome-scale metabolic models (GEMs) are mathematical representations of the metabolism of an organism that describe mass-balanced relationships between the metabolites of the organism. A key element of a GEM is the biomass composition, which specifies the metabolites consumed and produced by the cellular growth together with their corresponding stoichiometric weights. Although these weights are exact real numbers in most models, their actual values are usually uncertain. Hence, the accuracy of GEMs is limited by the presence of uncertain parameters, which can lead to poor predictions.

Here, we propose a particular class of Flexible Nets (FNs), called ENDI, to model and analyze this uncertainty. An event net with default intensities (ENDI) is a tripartite graph determining the net structure which, in addition to the stoichiometry, it also specifies potential intensity constraints. We show how a GEM can be transformed into an ENDI which can accommodate uncertain stoichiometric coefficients. The impact of uncertain coefficients on the growth rate of the organism can be assessed straightforwardly by an LPP derived from the ENDI. We have applied this method to several GEMs such as different types of bacteria, fungi and Chinese hamster ovary (CHO) cells. The results show that the growth rate increases monotonically with respect to the percentage of uncertainty. This is an expected result, since higher growth rates can be achieved if less biomass is required.

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TOWARD PATIENT-SPECIFIC SYSTEMS PHARMACOLOGY MODELS - APPLICATION TO GLIOBLASTOMA TREATMENT WITH TEMOZOLOMIDE

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Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults and is still incurable with an overall patient survival below 18 months [1]. In this context, a pharmacokinetic-pharmacodynamic (PK-PD) mathematical model of temozolomide (TMZ), the anti-tumor agent of choice against GBM, was developed in a previous study (in prep.). This model was initially calibrated on extensive data of a single GBM cell line: LN229. The aim of this project is to design a personalization methodology of this TMZ PK-PD model, to predict TMZ cytotoxicity of a given cell line, from its multi-omics data. We have developed the personalization methodology on a dataset built from four independent experiments collected in the literature, all conducted on commercial cell lines, for which transcriptome and proteome are available. Selected studies include TMZ cytotoxicity data for LN229 and other cell lines, LN18 or U87, for which we want to personalize the model. Model personalization involves re-calibrating certain parameters, then calculating initial conditions or cell-line-specific parameters. Particularly, we investigated how to infer semi-mechanistic model parameters related to a whole DNA repair pathway by creating inference rules of increasing complexity. Our findings revealed that the accuracy of parameter inference increased with the incorporation of prior knowledge. For instance, we used data from a genome wide CRISPER-Cas9 screen of GBM cells under TMZ exposure, from MacLeod et al [2], to identify genes that increase sensitivity or resistance to TMZ. From the best rule, we identified a minimal dataset required to infer parameters related to pathway activity in a given cell line. Once fully developed, such a patient-specific framework could be used to design personalized TMZ-based combination therapies. Combination therapies hold promise for improving patient survival, notably by bypassing the resistance mechanisms that prevent TMZ from being effective [3].

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INTERPLAY OF EXPLOITATIVE COMPETITIONS AND APPARENT COMPETITIONS - A CASE STUDY OF FIVE SPECIES ECOLOGICAL MODELS

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This work investigates a five-species predator-prey model with Lotka-Volterra functional response. The whole model is blended by one two-predators-one-prey model and two one-predator-two-preys models. It is well known that exploitative competition and apparent competition happen in the two-predators-one-prey model and the two-predator-two-preys model, respectively. So, some interesting questions are arising between the interplaying of these two indirect competitions. The mathematical analysis starts by recalling some results of three species. Then, the dynamics of all four species models are established. Finally, two extinction results are shown in the five species models.

EXPLORING COLORECTAL CANCER DEVELOPMENT AT THE CRYPT LEVEL WITH CONTINUOUS MATHEMATICAL MODELS

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Colorectal cancer poses a significant health challenge globally. Understanding the processes underlying its development is crucial for effective prevention and treatment. In this poster, we employ continuous mathematical modeling in three dimensions to explore the dynamics governing cancer development at the crypt level.

Crypts, microscopic structures within the colonic epithelial layer, regulate cell proliferation and differentiation, critical for colorectal homeostasis. Disruptions in these processes can lead to cancer development and mathematical modeling at this point can help to unravel the underlying mechanisms. A new methodology is presented to simulate cancer development in the human colon at the crypt level in three dimensions using partial differential equation models. First, a model based on elasto-growth equations is presented so that the crypts can be created in three dimensions in a natural way. In addition, population growth equations coupled with reaction diffusion equations are used to investigate how the resulting geometry can influence cancer development.

The poster shows preliminary insights into the simulation results and how continuous models can be used to understand cancer development at the crypt level. By refining our model parameters, we aim to enhance the accuracy of predictions regarding cancer growth dynamics based on epithelial structure. Beyond colorectal cancer, our approach holds promise for elucidating the mechanisms underlying various epithelial cancers and other pathologies characterized by dysregulated cell proliferation and differentiation.

CELL INVASION MODELS: HOW COMPLEX DO THEY NEED TO BE?

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The invasion of the extracellular matrix (ECM) by cancer cells is a highly complex process, but many mathematical models describing it are quite simple. This raises the questionhow these simpler models differ from the more complex ones regarding their dependence on input parameters and their qualitative results, and whether simpler models are able to capture and reproduce the results of complex models. To investigate these questions, three cell invasion models are examined: two simple to intermediate partial differential equation (PDE) models with six and eight parameters, respectively, and a complex hybrid model with 17 parameters. The hybrid model was originally developed for angiogenesis, featuring a Cellular Potts model and a finite element formulation, and is extended in this work to describe cell invasion as travelling waves. The models' parameter sensitivity with respect to three parameters is examined using a variance-based method at various points in time. At first, the PDE models exhibit mainly first-order effects from the initial ECM density, and later in time from the ECM degradation rate. At all points in time, the hybrid model is affected the most by the proliferation probability, and by interaction effects between all three parameters. The data fitting abilities are tested by generating data using the hybrid model and estimating the corresponding PDE model parameters. This is done under consideration of various phenomena and conditions. Using the fitted parameters, the shape approximations and velocities of the travelling invading waves are compared between the models. The best approximations in shape are performed by the PDE model with eight parameters, the best ones in wave speed are obtained using the model with six parameters. The main finding is that while the model outputs are relatively similar and can be approximated adequately by the PDE models, the hybrid model's dependence on its input parameters differs substantially from the PDEs'.

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THE ROLE OF INTRASPECIFIC TRAIT VARIATION (ITV) AND NICHE CONSTRUCTION BY PARASITES IN HOST DENSITY REGULATION

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Parasites are ecologically important because they can shape community structure through their effect on trophic interactions, competition, food webs and biodiversity. They play a role in host density regulation in addition to other mechanisms like competition and predation. Though intraspecific trait variation (ITV) is recognized in recent years to be of importance for ecological dynamics [1], the implications of ITV for host-parasite interactions have received less attention. ITV and niche mechanisms (niche construction, niche conformance and niche choice) [2] which operate at an individual level could have effects on the interaction between species and hence the population dynamics of the species. We specifically aimed at studying the effect of niche construction by a parasite on its host and ITV in both host and parasite for the host-parasite population dynamics. The mathematical modelling was motivated by an empirical example [3] with immunity variation in host (Gammarus pulex) individuals and infectivity variation in parasite (Acanthocephalan) individuals (sibships) serving as ITV in both the species. This system is known to involve host immunodepression by parasite (niche construction by parasite) upon infection. We hypothesized the virulence of the parasite to be a function of the infectivity of the parasite and immunity of the host. Incorporating the effects of nonlinear averaging, our model found ITV and niche construction to decrease the virulence, as observed empirically. Next, we investigated the effect on population dynamics by incorporating virulence into the Anderson-May model. We observed that increase in ITV in host and parasite (and niche construction) increased regulation of host by the parasite. Host regulation by parasites is a key aspect of host parasite population dynamics and the fact that ITV in host and parasite have a role in it could thus help in predicting more accurately the effects of parasite in ecological dynamics.

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SUPPORTING MATHEMATICAL RESEARCH ON BRAIN METASTASES: DATASETS OF HIGH-RESOLUTION MRI IMAGES WITH CLINICAL DATA

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The development of mechanistic mathematical models and artificial intelligence (AI) algorithms in neuro-oncology requires the use of medical images that allow us to quantify the size and other morphological characteristics of lesions, their temporal evolution and their response to treatments. This is fundamental for studies of brain metastases, the most common type of intracranial tumor associated with poor survival and prognosis, which occur in approximately 30% of all oncology patients. High volumes of data, if possible publicly available, are needed to develop mathematical and AI models.

To address this problem the Mathematical Oncology Laboratory (MOLAB) in cooperation of health care institutions, oncologists, radiologists in the context of a clinical study: the Open Brain Tumor dataset for mathematical and AI applications (OpenBTAI), released a first dataset in [1]. Now, a second collection substantially larger is described in this poster. This new contribution contains 1406 high-resolution imaging studies of 443 patients bearing 1526 BMs, and 1148 segmentation files with 2134 individual lesions. Every lesion was semi-automatically segmented using a matlab based tool developed by our team. Initially, the tumors were automatically delineated by using a gray-level threshold that was carefully chosen to identify the contrast-enhancing tumoral volume. Next we reviewed and corrected each segmentation, slice by slice, using a brushing/pixel-removing tool to ensure accuracy and precision. Every segmentation was cross-checked by the experts. In addition, to the original images and contours, morphological measurements and radiomic features for each segmented lesion are provided. This contribution enables the development and validation of predictive and prognostic models with clinical relevance, evaluation of disease status, and improved treatment planning methods.

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A MODIFICATION OF KUZNETSOV'S MODEL TO ACCOUNT FOR NONLINEAR INTERACTION

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Using Kuznetsov's model as a basis, we modify the interaction term between tumor and effector cells to account for nonlinear interaction in the tumor cell population, focusing specifically on the interaction with cytotoxic T cells. We introduce an exponent in the tumor cell population, which provides the possibility to account for scenarios such as the simultaneous killing of multiple antigenic tumor cells by a single cytotoxic T cell or to account for the surface of a solid tumor. The model can be used to study the response to T cell-based cancer immunotherapies. Using the exponent as the bifurcation parameter, one can show the existence of a Hopf bifurcation. By adjusting this parameter, one could potentially regulate the oscillatory behavior of solution curves in proximity of the locally asymptotically stable non-trivial equilibrium, potentially improving data fitting and outcome prediction.

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THE ROLE OF PERSISTENT INFLAMMATION IN HEMATOPOIETIC DYNAMICS AND DISEASE EVOLUTION

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Hematopoiesis, the process of blood cell generation from Hematopoietic stem cells (HSC), is intricately regulated by cytokine-mediated feedback mechanisms. This study delves into the impact of inflammation on normal hematopoiesis and its role in the progression from health to Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML). Our findings highlight the substantial influence of persistent inflammation on hematopoietic disease dynamics, offering insights into potential therapeutic avenues.

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