

2018 Annual Meeting of the Society for Mathematical Biology & the Japanese Society for Mathematical Biology

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Book of Abstracts

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Optimal control with multiple human papillomavirus vaccines

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Many human papillomavirus (HPV) vaccination programs currently administer three vaccines - a bivalent, a quadrivalent and a nonavalent vaccine - for a two-dose course. In this talk a model will be presented to explore optimal vaccination strategies using the three vaccines, which differ in protection breadth, cross-protection, and type-specific efficacy. Assuming the HPV infection prevalence in the population under the constant vaccination regime, optimal control theory will be used to discuss optimal vaccination strategies for the associated non-autonomous model when the vaccination rates are functions of time. The impact of these strategies on the number of infected individuals and the accumulated cost will be assessed and compared with the constant control case. Switch times from one vaccine combination to a different combination including the nonavalent vaccine will be assessed during an optimally designed HPV immunization program.

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Mathematics of climate change and malaria transmission dynamics

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Climate change is known to significantly affect the dynamics of vector-borne diseases, such as malaria. In particular, the species involved in the transmission dynamics of malaria are affected by various abiotic conditions, such as temperature, precipitation, humidity and vapor pressure. A number of models, typically statistical (using data and statistical approaches to correlate some climate variables with malaria incidence) or mechanistic (accounting for the detailed dynamic nonlinear processes involved in disease transmission), have been employed to assess the likely impact of anthropogenic climate change on malaria transmission dynamics and control. These models have (generally) reached divergent conclusions, with some predicting a large expansion in the continental land area suitable for transmission and in the number of people at risk of malaria, while others predict only modest poleward (and altitudinal) shifts in the burden of disease, with little net effect, and the issue remains unresolved thus far. I will discuss some of our recent results on modelling the effect of climate variables (notably temperature) on the dynamics of malaria vector and disease.

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Mathematics of a sex-structured model for Syphilis transmission dynamics

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Syphilis, a major sexually-transmitted disease, continues to pose major public health burden in both under-developed and developed nations of the world. This study presents a new two-group sex-structured model for assessing the community-level impact of treatment and condom use on the transmission dynamics and control of syphilis. Rigorous analysis of the model shows that it undergoes the phenomenon of backward bifurcation. In the absence of this phenomenon (which is shown to arise due to the re-infection of recovered individuals), the disease-free equilibrium of the model is shown to be globally-asymptotically stable (GAS) when the associated reproduction number is less than unity. Furthermore, the model can have multiple endemic equilibria when the reproduction threshold exceeds unity. Numerical simulations of the model, using data relevant to the transmission dynamics of the disease in Nigeria, show that, with the assumed 80% condom efficacy, the disease will continue to persist (i.e., remain endemic) in the population regardless of the level of compliance in condom usage by males. Furthermore, detailed optimal control analysis (using Pontryagin's Maximum Principle) reveals that for situations where the cost of implementing the controls (treatment and condom-use) considered in this study is low, channeling resources to a treatment-only strategy is more effective than channeling them to a condom-use only strategy. Furthermore, as expected, the combined condom-treatment strategy provides a higher population-level impact than the treatment-only strategy or the condom-use only strategy. When the cost of implementing the controls is high, the three strategies are essentially equally as ineffective.

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Global stability of some continuous and nonstandard discretization models for the Ebola virus disease with fast and slow transmissions

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Mathematical models for the Ebola Virus Disease (EVD) were, until recently, mostly based on the fast/direct transmission route, which involves contact with blood or body fluid and objects that have been contaminated by body fluid. The fact that in almost all outbreaks of the EVD in Africa, the index case became infected through contact with infected animals, such as fruit bats and primates, makes the environment a no negligible channel for slow/indirect transmission of the disease.

In this talk, we incorporate both direct and indirect transmission routes in the setting of SIR-type models that are developed gradually. Firstly, we add two compartments (for dead individuals and for the environment) in order to capture infection through the manipulation of deceased individuals before burial as well as contaminated environment. Secondly, we enrich the first model with self-protection measures reflected by the addition of classes of vaccinated and trained individuals.

For the two models, we prove that the disease-free equilibrium is globally asymptotically stable (GAS) whenever the basic reproduction number is less than or equal to unity, and unstable when this threshold number is greater than 1. In the latter case, the existence of at least one endemic equilibrium (EE) (for the second model) and of a unique EE (for the first model), which are locally asymptotically stable (LAS) is shown, together with the fact that the unique EE is GAS in the absence of shedding and manipulation of deceased human individuals before burial. At the endemic level, it is shown that the number of infectious individuals is much smaller than that obtained in the absence of any intervention.

In a final step, we construct nonstandard finite difference schemes that are dynamically consistent with respect to the above features of the continuous models.

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Dengue dynamics in Southern Mexico: an approximation to its population dynamics and the role of population movement

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Using a data base on Dengue incidence available for four different states of the country we develop mathematical models that describe the recurrent dynamics of cases at different geographical/regional levels. We present preliminary results.

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Signatures of within-host dynamics of dengue at a population level

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Vector-borne diseases cause worldwide concern with hundreds of millions of new cases and over a million deaths reported annually. Mathematical models are a key tool in the study of the spread of diseases such as malaria and dengue. In particular, transmission models have been successful at determining the most promising intervention strategies, despite the fact that many of these models assume all individuals experience identical infections. Within-host dynamics of infections, however, vary widely among individuals. In the case of dengue, within-host dynamics differ between primary and secondary infections, where secondary infections with a different virus serotype typically last longer, produce higher viral loads, and induce more severe disease. Here, we build upon models of variable within-host dengue virus dynamics resulting in mild dengue fever and severe dengue hemorrhagic fever by coupling them to a population-level model. The resulting multiscale model examines the dynamics of between-host infections in the presence of two circulating virus strains that involves feedback from the within-host and between-hosts scales. We analytically determine a threshold under which infections persist in the population.

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Population epidemiology under toxicant stress: a nested multi-level modelling framework

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Populations are formed of their constituent interacting individuals, each with their own respective within-host biological processes. Infection not only spreads within the host organism but also spreads between individuals. We propose and study a nested multilevel model which links the within-host statuses of immunity and parasite density to population epidemiology under sub-lethal and lethal toxicant exposure. We analyse this nested model in order to better understand how toxicants impact the spread of disease within populations. We demonstrate that the outbreak of infection within a population is completely determined by the level of toxicant exposure, and that it is maximised by intermediate toxicant dosage. We classify the population epidemiology into 5 phases of increasing toxicant exposure and calculate the conditions under which disease will spread, showing that there exists a threshold toxicant level under which epidemics will not occur. In general, higher toxicant load results in either extinction of the population or outbreak of infection. The within-host statuses of the individual host also determine the outcome of the epidemic at the population level. We discuss applications of our model in the context of eco-epidemiology, particularly for bee colony losses, predicting that increased exposure to toxicants could result in more epidemics and therefore greater colony losses. We predict that reducing sub-lethal toxicant exposure below our predicted safe threshold could contribute to controlling population level disease and infection.

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Identifying differences in the rules of interaction between individuals in moving animal groups

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The spectacular patterns of collective animal movement have been, and remain, a long standing and major interest in many branches of science, including biology, mathematics, physics and computational science. It is thought that the emergent patterns of coordinated motion are the consequence of individuals applying simple rules to adjust their velocity based on the relative locations and movements of nearby group members.

From the early 1980s onwards, the dominant methods for examining hypotheses about simple rules of interaction leading to coordinated, and sometimes complex, group motion have been discrete time self-propelled particle models. Common to many of these models are interaction rules chosen such that individuals will adjust their velocity to: avoid collisions with nearby neighbours, align their direction of motion with group members located at intermediate relative distances, and move towards other group members that are at relatively greater distances.

In the last decade advances in automated visual and GPS tracking methods have led to the exciting development of techniques for estimating the local rules of interaction used by real animals to coordinate collective motion directly from observational data. Analysis of tracking data, particularly of birds or fish in motion, suggests that the form of interaction rules chosen in self-propelled particle models is indeed plausible, with real animals adjusting their velocities consistent with collision avoidance at short range, matching directions of motion, and attraction to distant group mates. However, the mechanics of real interactions differ in detail to those adopted in models, even if the broad principles appear the same.

In this talk I will discuss an averaging technique for estimating how individual's adjust their velocity as a function of the relative coordinates of their partners, and potentially other independent variables,

directly from tracking data. Such techniques were first developed in concurrent studies by Katz *et al.* [1] and Herbert-Read *et al.* [2], and have since been further refined (see for example, [3]). I will then present some results that illustrate some of the commonalities and differences seen in the rules of interaction of different species of shoaling fish. I will discuss how randomisation methods can be used to identify when there are statistical differences in observed interaction rules of individuals belonging to different categories (for example hungry animals versus those that have recently fed to satiation). Finally, I will use these methods to examine differences in interaction rules between pairs of fish where one fish dominates leadership positions, and the other follows.

[1] Katz *et al.* *PNAS*, 108:18720-18725, (2011)

[2] Herbert-Read *et al.* *PNAS*, 108:18726-18731, (2011)

[3] Schaerf *et al.*, *Science Advances*, 3:e1603201, (2017)

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Modelling Carpageddon - the deliberate release of CyHV-3

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The deliberate release of Cyprinid herpes virus 3 (CyHV-3) to control invasive common carp (*Cyprinus carpio*) in the Murray-Darling Basin of south-eastern Australia has been dubbed 'Carpageddon' and is highly controversial. Common carp now represent up to 90% of the biomass in invaded waterways and mortality rates of 70-80% have been observed during outbreaks of CyHV-3 in the northern hemisphere. Hence, the release of CyHV-3 carries the risk that decomposition following mass-mortality of carp may lead to severe oxygen depletion and subsequent anoxic events. I will present mathematical modelling that is the basis for (i) developing a low-risk release strategy, and (ii) advice to the Australian government on the long-term benefits of releasing the virus. The model couples a stage based demographic model with an SEIR-type model; recruitment of young carp is determined by available spawning habitat and the river system hydrology. We show that the long-term virus impact and the dynamics predicted by the model depend largely on the presence of a latent class that allows for virus reactivation and onward infection. The impact of CyHV-3 is also sensitive to where density-dependence occurs in the life cycle of carp because of the potential for virus mortality to either replace, or be in addition to, density-dependent mortality.

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Epidemiological consequences of different vaccination strategies against infectious diseases in domestic livestock

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A vaccine is a biological preparation, providing long-term protection of the host to a disease by miming the interactions between the pathogen and the immune response. For decades vaccines have been the most effective means to fight and eradicate infectious diseases, from human diseases to

animals diseases, including poultry and porcine viruses. One of the most significant endemic swine disease causing major animal and economic losses all over the world is porcine reproductive and respiratory syndrome (PRRS). Although different types of vaccines are on the market and various vaccination strategies have been trialled to control the disease, PRRS continues to persist, sometimes at high prevalence. The failure of some vaccination strategies to combat the disease leaves open questions regarding the major effect that the vaccine should have, as well as the most efficient vaccination strategy. We present an SIR model of a non-vaccinated population and extend it to a model where vaccination is applied. We use numerical simulations to evaluate vaccine efficacy for different types of vaccines and vaccination strategies to predict determinants for disease prevention. The study provides important guidelines for vaccine development and application in livestock populations.

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Immune selection of malaria quasi-species

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Multiple selective pressures drive evolution of malaria parasite, and determine its phenotypic traits, like virulence, transmissibility, drug resistance, as well as its population structure in host communities. Immune regulation plays an important part in this process, both within-host and on population level. The key to parasite survival within host is its antigenic variation, whereby parasite can avoid immune clearing by switching on and off multiple antigenic variants. In *P. falciparum* species, this process is controlled by a multigene var family, expressed on infected erythrocytes.

To study within-host parasite-immune interactions and the resulting selection processes we develop an agent based approach, that accommodates most salient features of malaria infection - RBC depletion, immune stimulation and clearing, antigenic variation.

In our setup, each parasite strain has a specific genetic makeup (collection of var genes), drawn from a large pool. Multiple strains of such quasi-species, compete within-host via cross-reactive immunity. Furthermore, mixed strains can recombine in mosquito agent to produce new types. Parasite diversity in host population can change in response to external factors, intensity of transmission and host immune status.

We apply our model to examine individual and population level outcomes, and quantify the relationship between environmental inputs (intensity of transmission, immune competence), and the evolution of parasite population structure.

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The coevolution of transitive inference and memory capacity in the hawk-dove game

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Transitive inference (TI) that uses known relationships to deduce unknown ones (using $A > B$ and $B > C$ to infer $A > C$ given no direct interactions between A and C) to assess the opponent's strength, or resource-holding potential (RHP), is widely reported in animals living in a group. This sounds counter-intuitive because the mechanism of TI seems to require social cognition and large memory

capacity; individuals, in the TI mechanism, need abilities to identify others, observe contests among others and keep the results in memory. We examine the coevolution of memory and transitive inference by the evolutionary simulations, using the asymmetric hawk-dove game when a cost for losers is higher than a reward for winners. We found that the immediate inference strategy (II), which estimates the opponent's strength based on the past history of the direct fights, evolves with the large memory capacity, while the TI strategy, which estimates the unknown opponent's strength by transitive inference, evolves with the limited memory capacity. When a cost for losers is slightly higher than a reward for winners, the II strategy with the large memory capacity has an evolutionary advantage over the TI strategy with the limited memory capacity. It is because the direct fights are not so costly that more information about the fights leads to more accurate estimation of the opponent's strength and results in the accurate rank of the RHPs. When a cost for losers is much higher than a reward for winners, the TI strategy with the limited memory capacity has an evolutionary advantage. It is because a good way to avoid the costly fights is the prompt formation of the dominance hierarchy which does not necessarily reflect the actual rank of the RHPs; the TI strategy builds the dominance hierarchy much faster than the II strategy regardless of memory capacity, and the large amounts of information are not required for the TI strategy to form the dominance hierarchy promptly. Our study suggests that even smaller memory capacity is evolutionarily favoured in TI. The TI strategy tends to reinforce the hierarchy once it is built, regardless of whether it is consistent with RHP or not, because results of direct fights are always counted. Smaller memory capacity allows players to adjust the hierarchy well if it does not represent RHP. These results prove that TI can evolve in animals, which do not have the large memory capacity.

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Topology-dependent density optima for efficient simultaneous network exploration

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From the foraging strategies of large organisms, to T-cells hunting pathogens, to proteins examining strands of DNA, carefully optimised search processes are a phenomenon that pervades throughout nature at many scales. Often these search processes do not proceed in isolation, but instead many instances proceed in parallel, competing for space and resources. In this talk I shall discuss optimisation of search processes on networked topologies where the searchers interact with each other through competition for space. Taking the simple exclusion process as the fundamental model for spatial interactions, I consider search strategies that seek to minimise the average cover time for individuals that search in parallel. We will see that the optimal strategy is to implement parallel searching at an optimal density of searchers that depends heavily on the given network topology, and that the optimal density can be well predicted by the spectral gap of the network. These results are verified over a broad class of networks, as well as real-world transport networks such as the London tube network. I will conclude by considering an asymmetric search process that reveals unexpected changes in efficiency between classes of networks.

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The remarkable simplicity of complex signalling networks

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Robustness, and the ability to function and thrive amid changing and unfavourable environments, is a fundamental requirement for all living systems. Moreover, it has been a long-standing mystery how the extraordinarily complex communication networks inside living cells, comprising thousands of different interacting molecules, are able to exhibit such remarkable robustness since complexity is generally associated with fragility. In this talk I will give an overview of our recent research on robustness in cellular signalling networks, with an emphasis on the robust functionality known as Robust Perfect Adaptation (RPA). Our work has now suggested a resolution to the complexity-robustness paradox through the discovery that robust adaptive signalling networks must be decomposable into topological basis modules of just two possible types. This newly-discovered modularisation of complex bionetworks has important implications for evolutionary biology, embryology and development, cancer research and drug development.

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Calcium dynamics within the nuclei of cardiac muscle

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Cardiovascular disease is the leading cause of death in Australia; responsible for 30% of deaths. Diseases that affect the heart are commonly accompanied by a condition known as hypertrophy — heart enlargement through cell growth. This condition leads to uneven heart beats and, eventually, heart failure.

Hypertrophy is regulated by the flow of calcium ions within the cell. Calcium dynamics control the activation of the proteins required for hypertrophic gene expression and their localisation to the cell nucleus. However, there has been little research done on calcium flow within the nuclei of normal heart cells let alone those of diseased hearts.

We focus specifically on modelling the mechanics of calcium flow within the nucleus and distinguishing the signal for heart cell growth in the nucleus where gene expression takes place over the background signal for the heartbeat. Using a finite element model, we describe the spatiotemporal properties of these background calcium oscillations as they propagate into the nucleus. We verify this model with existing data to produce a clearer picture of the calcium dynamics involved in initiating hypertrophy.

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Parameter estimation of an S-system model using hybrid genetic algorithm with the aid of sensitivity analysis

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A biochemical system is a biological system consisting of a collection of chemical compounds interacting with each other. One way to model and analyze a biochemical system is by using S-systems, which are coupled ordinary differential equations based on power-law formalism. In this work, we

do a parameter estimation on an S-system model called HS96. This model, proposed by Hlavacek and Savageau in 1996, describes a simple genetic network consisting of five dependent variables X_i , $i = 1, 2, \dots, 5$. As a preliminary method, sensitivity analysis of HS96 is conducted to investigate the change in model outputs with respect to the changes in model parameters. Usual model outputs are X_i and \dot{X}_i , $i = 1, 2, \dots, 5$. From the results of sensitivity analysis, model outputs are selected which are then used to estimate the parameters of the HS96 model. A hybrid of genetic algorithm with the interior point method is used in the parameter estimation.

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Patterning in development and the role of short and long range signalling

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Many biological systems rely on both long range and short range signals in order to produce proper cell patterns during development. These patterns, such as alternating cell fates, are defined by different gene and protein expression levels. However, the relative contribution of these two signalling modes in establishing proper patterns is not well understood. Using vulval development of two nematode worm species, *C. elegans* and *C. briggsae*, as motivation, we derive an asymptotic PDE based on a simplified signalling network consisting of EGF, Notch and Wnt. We demonstrate that additional long range signals can provide a framework for understanding species-specific differences and that variations in short range signalling can amplify long range signals. These results suggest that long and short range signals have critical roles to play in proper cell patterning in development. This work is joint with Helen Chamberlin and Carly Williamson.

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Crosstalk in transition: Akt translocation as a damped harmonic oscillator

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Akt/PKB (Protein Kinase B) is a major crosstalk node in the mammalian cell. Located at the juncture of several key signalling pathways, it is involved in many cellular processes, such as glucose metabolism, cell growth and the suppression of apoptosis. Dysregulated Akt signalling is implicated in a range of human disorders, from diabetes to cancer.

Initially, Akt is synthesised in the unactivated state on the endoplasmic reticulum. However, the activation (phosphorylation) of Akt in response to insulin stimulation only occurs at the plasma membrane, necessitating the translocation of Akt from the interior to the periphery of the cell. At the moment, the understanding of this translocation process is still in its infancy, but there are some indications that it is a staged process.

We have developed a deterministic, three-compartment, ordinary differential equation (ODE) model of Akt translocation. Given a conservation relation implicit in the model, it can be shown that this system is equivalent to the damped harmonic oscillator equation; a classic, well-studied ODE. With this framework, we investigate the different modes of downstream signalling that can be produced by the model and the conditions for their manifestation.

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Investigating the role of iron in cancer progression via a multi-scale computational model

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It is becoming increasingly clear that tumour cells recruit cells in their surrounding microenvironment to aid in their proliferation. Tumour-associated macrophages and stromal cells are now believed to play a prominent role in tumour growth. Some evidence points to the fact that iron is a key player in the complex interactions between cancer cells and the microenvironment. This talk will present a computational model of tumour growth investigating the role of iron and the tumour microenvironment in tumour progression. Furthermore, the talk will describe how data gathered from a bioprinter will be used to calibrate the model.

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Optimal control analysis of a mathematical model for breast cancer

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In this paper, a mathematical model of breast cancer governed by a system of ordinary differential equations in the presence of chemotherapy treatment and ketogenic diet is discussed. Several comprehensive mathematical analysis was carried out using varieties of analytical methods to study the stability of the breast cancer model. Also, sufficient conditions on parameter values to ensure cancer persistence in the absence of anti-cancer drugs ketogenic diet and cancer emission when anti-cancer drugs, immune-booster, ketogenic diet are included were established. Furthermore, optimal control theory is applied to find out the optimal drug adjustment as an input control of the system therapies to minimize the number of cancerous cells by considering different controlled combinations of administering the chemotherapy agent and ketogenic diet using the popular Pontryagin's Maximum Principle. Numerical simulations are presented to validate our theoretical results.

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Predicting the response of breast cancer to neoadjuvant chemotherapy with an imaging-driven, mechanics-coupled, reaction-diffusion model accounting for patient-specific therapeutic regimens

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Clinical methods for assessing tumour response to neoadjuvant therapy largely rely on monitoring the temporal changes in tumour size. Our goal is to predict tumour response to neoadjuvant therapy in breast cancer using a mathematical model that utilizes non-invasive imaging data obtained from individual patients. Previously, a mechanically-coupled, reaction-diffusion model with logistic growth for breast cancer was shown to outperform clinically used measures for predicting tumour response to therapy when initialized with patient specific magnetic resonance imaging (MRI) data. This model has since been extended to include patients' therapy using corresponding dynamic contrast-enhanced (DCE-) MRI data to determine areas for drug delivery, improving the concordance correlation coefficient of the predicted tumour cellularity compared to the calculated cellularity from 0.85 to 0.99 ($p < 0.01$, $N=5$).

We use patient specific measurements from diffusion-weighted MRI data to calibrate tumour cell diffusion, carrying capacity, and proliferation values (on a per voxel basis) within each patient's tumour domain. The model is 3D and is mechanically coupled to the properties of the breast tissues by dampening the diffusivity of tumour cells based upon their growth and stresses induced in the breast. DCE-MRI data is used to identify spatiotemporal variations in tumour perfusion to approximate delivery of therapy within the tumour using the extended Kety-Tofts model. An explicit death term is incorporated into the tumour cell equation, where the amount of drug distributed in the tissue is spatially heterogeneous and dynamic in time according to the patient's therapy schedule. All model simulations were evaluated using a forward finite difference scheme.

For a cohort of breast cancer patients ($N = 10$), four MRI scans were collected over the course of their neoadjuvant therapy (pre-treatment, after one cycle of therapy, at the end of the first therapy, and after one cycle of the second therapy). Using this data, we assess the model's predictive ability in two different ways: 1) using the first two scans, the model is calibrated and simulated forward to the third scan time to assess the tumour cellularity, size, and heterogeneity predicted by the model in comparison with the calculated values from the patient's third scan; 2) the model is calibrated with the third and fourth scans and simulated forward to the time of surgery, where the model's results are compared to the patient's pathological response status. Using these metrics, we will report on and discuss ability of the modelling approach to predict tumour response to therapy in breast cancer.

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Evolutionary cancer therapy

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Heterogeneity in cancer is increasingly being recognized as a key determinant of tumour progression and response to therapy. However, much of our current understanding of this heterogeneity has been driven by our ability to measure it, and therefore has largely focused on the genomic scale. Ultimately such heterogeneity is realized through the generation of distinct phenotypes. In recent years there has been a deeper appreciation for how phenotypic variation is modulated by a range of

biological mechanisms over different spatial scales - specifically epigenetic, metabolic and microenvironmental. Within a growing tumour, multiple cellular phenotypes and a spatiotemporally-varying microenvironment form a complex ecosystem that exhibits unintuitive, nonlinear behaviour.

Treatment of advanced cancers has benefited from new agents that supplement or bypass conventional therapies. However, even effective therapies fail as a heterogeneous tumour cell population deploys a wide range of resistance strategies. We propose that evolutionary dynamics ultimately determine survival and proliferation of resistant cells, therefore evolutionary treatment strategies should be used with conventional therapies to delay or prevent resistance. Using an agent-based framework to model spatial competition among sensitive and resistant populations, we apply anti-proliferative drug treatments to varying ratios of sensitive and resistant cells. We compare a continuous maximum tolerated dose schedule with an adaptive schedule aimed at tumour control through competition between sensitive and resistant cells. We find that continuous treatment cures mostly sensitive tumours, but with any resistant cells, recurrence is inevitable. We identify two adaptive strategies that control heterogeneous tumours: dose modulation controls most tumours with less drug, while a more vacation-oriented schedule can control more invasive tumours.

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Discriminating response across treatments using the patient-specific model-derived days gained metric

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Accurate clinical assessment of a patient's response to treatment is a critical task in the era of precision medicine. Glioblastoma (GBM), a primary brain tumour with dismal median survival times of 12-16 months, has a highly heterogeneous, invasive profile, causing tumour dynamics and therapeutic response to vary widely from patient to patient. Currently, two sets of standard assessment criteria are used, RANO and iRANO (for standard radiation and chemotherapy versus immunotherapy, respectively), for evaluating changes in tumour size following treatment to determine whether a patient responded to that treatment. In addition, when complex imaging transformations, such as pseudo-progression, occur in response to therapy these metrics require long follow-up times of 3-6 months. Therefore, it has been difficult for physicians to use existing metrics to define optimal treatment schedules, including when to maintain or switch therapies.

Using the Proliferation-Invasion (PI) model, the unique kinetics of individual patients' tumours can be simulated using derived rates of cell proliferation (ρ) and invasion (D) from serial magnetic resonance imaging (MRI). These models serve as untreated virtual controls of tumour growth, enabling comparisons against post-treatment imaging to generate a patient-specific "Days Gained" (DG) response metric. DG values were evaluated across a variety of primary and secondary therapies for thresholds discriminating long and short-term survivors.

Significant DG thresholds were found using follow-up imaging 1-2 months post therapy in patients receiving cytotoxic, radiation, and immunotherapeutic treatments. High DG thresholds were associated with better survival in standard radiation and chemotherapy treatments. In contrast, low DG values were discriminative of longer survival for immunotherapy due to the well known pseudo-progression effect of image-detectable inflammation response. The DG metric therefore demonstrated utility as a single, patient-specific method for judging response across multiple therapies with different response profiles that currently require distinct evaluation criteria (RANO and iRANO respectively). In addition, Days Gained was assessable in a similar or shorter time window than the

existing metrics. Taken together, these data support the utility of the model-derived response metric, Days Gained, in a diversity of clinical settings to quantitatively connect response with patient survival.

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Mathematical modelling for cancer recurrence caused by premalignant lesions formed before the first treatment

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Residual premalignant lesions after the first treatment such as surgery and chemotherapy are considered to be a cause of cancer recurrence. A previous study showed that the presence of premalignant lesions surrounding the primary tumour drives the high rate of local cancer recurrence. If cancerization requires m specific mutations in one cell, cells which have less than m mutations are still not cancer cells but have higher risk of cancerization than normal cells. In this study, we constructed a mathematical model of cancer recurrence caused by premalignant lesions ($m=2$ in this model). There are three populations in the model: (i) normal cells with no mutation, (ii) premalignant cells with one mutation, and (iii) cancer cells with two mutations. The total number of a healthy tissue is kept constant and there is a rare chance of mutation every time cell divides. Once a cancer cell with two mutations arises, the population proliferates exponentially, ignoring the number restriction. Under this assumption, we investigated the dynamics of accumulating mutations by combining Moran process and branching process. As a result, we derived analytical solutions for the probability distribution of the number of cancer cells over time and confirmed the accuracy by comparing them to the results from stochastic simulations. Finally, we found that premalignant lesions have a greater effect on time to recurrence when patients are older or growth rate of cancer cells is lower.

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Mathematical modelling of the immune response to cancer: an individual based approach

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The advances in cell imaging technology has allowed for deeper understanding of the movement mechanisms of immune cells. Experimental evidence suggests that cytotoxic T lymphocytes and dendritic cells undergo and unrestricted search motion until they switch to a more restricted motion induced by activation by tumour antigens. This change in movement is not often considered in the existing mathematical models of the interactions between immune cells and cancer cells. We present a spatially structured individual-based model of tumour-immune competition that takes explicitly into account the difference in movement between inactive and activated immune cells, using Lévy walks and Brownian motion to capture this motion, respectively. The effects of activation of immune cells, the proliferation of cancer cells and the immune destruction of cancer cells are also included in the model. We illustrate the ability of our model to reproduce qualitatively the spatial trajectories of immune cells observed in experimental data of single cell tracking. Computational simulations of our model further clarify the conditions for the onset of a successful immune action against cancer cells and suggest possible targets to improve the efficacy of cancer immunotherapy.

Overall, our theoretical work highlights the importance of taking into account spatial interactions when modelling the immune response to cancer cells.

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An experimental-computational approach for predicting the spatial-temporal response of tumour and vasculature to radiation therapy

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Introduction. Radiation therapy is a critical portion of the standard-of-care for patients with brain tumours, as it targets residual disease and non-operable tumours. However, one of the shortcomings of radiation therapy is the heterogeneity of response observed in the patient population which may be due to fundamental limitations in the way radiation therapy plans are currently selected. To this end, we are developing a coupled system of biophysical models of tumour growth and angiogenesis to predict the spatial-temporal response to radiation therapy within a tumour that is initialized and calibrated on an individual basis from non-invasive magnetic resonance imaging (MRI) data.

Methods. To evaluate this model system, we use subject-specific diffusion-weighted MRI (DW-MRI) and dynamic contrast enhanced MRI (DCE-MRI) acquired at seven time points (collected every 48 hrs) in rats ($n = 7$) with C6 gliomas. Three imaging time points (t1-t3) were acquired before the rats received a single fraction of either 20 Gy ($n = 4$) or 40 Gy ($n = 3$) dose of x-ray radiation delivered over the whole brain, while the remaining time points (t4 - t7) were collected post-treatment. DCE-MRI data was used to identify tumour regions of interest and estimate the blood volume fraction (vb) on a voxel basis. Tumour cell number (Ntc) was estimated using DW-MRI data. The spatial-temporal evolution of Ntc and vb in 3D was described by two coupled, partial differential equations describing the motility, proliferation, and death of tumour cells and blood vessels. Model parameters were calibrated from data on t1-t4, which were then used in a forward evaluation of the model from t5-t7. Error was assessed by calculating the percent error in the predicted and observed tumour volume. Agreement between the spatial distributions of Ntc and vb was assessed by calculating the concordance correlation coefficient (CCC) between the measured and observed quantities.

Results. For the rats that received 20 Gy of radiation, the error between the predicted and observed tumour volume ranged from 6% to 13% from t5 to t7. Additionally, the CCC between the predicted and observed Ntc ranged from 0.65 to 0.73 for all rats, while the CCC for vb ranged from 0.47 to 0.85. Higher error was observed for the rats who received 40 Gy of radiation, where the error between the predicted and observed tumour volume ranged from 10% to 18% on days t5-t7. A high level of agreement CCC greater than 0.70 was observed on t5 for both the vb and Ntc, while CCCs less than 0.5 were observed on t6 and t7.

Conclusion and Discussion. The results of this study indicate the potential to accurately model the spatial-temporal evolution of tumour and blood volume fractions from clinically relevant imaging data following radiation therapy. Further development of subject-specific mathematical models, such as the one presented here, will facilitate individualized radiation therapy plans to address the heterogeneity of response to treatment.

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A mathematical light on initiation of colorectal and intestinal cancer

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Rapidly dividing tissues, like intestinal crypts, are frequently chosen to investigate the process of tumour initiation, because of their high rate of mutations. To study the interplay between normal and mutant as well as immortal cells in the human colon or intestinal crypt, we developed a 4-compartmental stochastic model for cell dynamics based on current discoveries. Recent studies of the intestinal crypt have revealed the existence of two stem cell groups. Therefore, our model incorporates two stem cell groups (central stem cells (CeSCs) and border stem cells (BSCs)), plus one compartment for transit amplifying (TA) cells and one compartment of fully differentiated (FD) cells. However, it can be easily modified to have only one stem cell group. We find that the main deficiency occurs when CeSCs are mutated, or an immortal cell arises in the TA or FD compartments. The probability of a single advantageous mutant CeSC being able to transform all cells into mutants is more than 0.2, and one immortal cell always causes all FD cells to become immortals. Moreover, when CeSCs are either mutants or wild-type individuals, their progeny will take over the entire crypt in less than 100 days if there is no immortal cell. Unexpectedly, if the CeSCs are wild-type, then non-immortal mutants with a higher fitness are washed out faster than those with a lower fitness (net reproduction rate). Therefore, we suggest one potential treatment for colon cancer might be replacing or altering the CeSCs with the normal stem cells.

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Control of prokaryotic cell division by Turing patterns

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Cell division requires the precise placement of the division ring at mid-cell to ensure both daughter cells are viable. However, the mechanisms behind this localization remain poorly characterized. There are a limited number of known ways to identify the centre of the cell. One such mechanism is a Turing pattern. One intracellular Turing pattern has been identified, that produced by the Min protein system. In *Escherichia coli*, the Min protein system plays a role in establishing the division ring position. Membrane-bound Min proteins form an oscillating spatial pattern where the proteins are concentrated at one pole of the cell and then another, leaving a barezone at the centre of the cell where the FtsZ ring will form. Based on molecular interactions of the Min system, we have formulated a mathematical model that reproduces Min patterning during cell growth and division. This model provides a platform to explore how the Min system functions and what characteristics are likely to be shared with other Turing patterning systems, should they exist. We examine the general characteristics of Turing patterns produced by the Min system. In particular, patterning approximates a harmonic of the cell shape and selects the dominant harmonic in a predictable manner. This shows what alternative intracellular Turing patterning systems are likely to appear and how they would behave in relation to cell shape. The oscillations of the Min system are shown to be translated into a mid-cell localization signal via the harmonics generated by non-linear interactions of the system. We show that division plane orientation in the pleomorphic archeon *Haloferax volcanii* can be predicted from cell shape by assuming that it is dictated by a Turing mechanism. This work makes progress towards understanding how the Min system functions to regulate cell division. More generally it develops tools to identify alternative Turing patterning systems and to understand how patterning can be translated into localization signals.

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Shape, length and location of PAR polarity in asymmetric cell division**Author:** Sungrim Seirin-Lee¹¹ *Hiroshima University***Corresponding Author:** seirin@hiroshima-u.ac.jp

Anterior-posterior (AP) polarity formation of cell membrane proteins plays a crucial role in determining cell asymmetry, which depends not only on the several genetic process but also biochemical and biophysical interactions. In *Caenorhabditis elegans*, a single fertilized egg cell (P0), its daughter cell (P1), and the germline precursors (P2 and P3 cells) form two exclusive domains of PAR proteins on the membrane along the anterior-posterior axis. Since a mother cell divides into two dissimilar daughter cells with different properties using this polarity, the shape and length scale of PAR domains are critical. Furthermore, the phenomenon of polarity reversal has been observed in which the axis of asymmetric cell division of the P2 and P3 cells is formed in an opposite manner to that of the P0 and P1 cells. The extracellular signal MES-1/SRC-1 has been shown to induce polarity reversal, but the detailed mechanism remains elusive. Here, I explore the mechanism of symmetry breaking and AP polarity formation using self-recruitment model of posterior proteins and show how the shape, length and location of PAR polarity can be formed robustly. If time is allowed, I also introduce a multi-dimensional polarity model including cell's geometrical property and show how the cell geometry can give a critical effect on AP polarity.

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Mathematical modelling and genetic analysis of the wave of differentiation in the fly brain**Author:** Makoto Sato¹¹ *Kanazawa University***Corresponding Author:** makotos@staff.kanazawa-u.ac.jp

During development of multicellular organisms, multiple signalling systems play important roles. However, it is very hard to understand the interplays between many signalling pathways using conventional methods of molecular biology, biochemistry and genetics. Mathematical modelling should be combined with these biological methods to solve biological problem.

The waves of differentiation in visual system development are key examples of the complex interplays between multiple signalling systems. In this study, we focus on a wave of differentiation called the proneural wave, which occurs in the developing fly brain and accompanies Notch-mediated lateral inhibition and EGF-mediated neural differentiation. During proneural wave progression, the sheet-like neuroepithelial cells (NEs) sequentially differentiate to neural stem cells called neuroblasts (NBs). The proneural wave is an ideal model system to investigate the roles and dynamics of the interplay between important signalling pathways such as Notch and EGF.

Notch-mediated lateral inhibition regulates binary cell-fate choice, resulting in salt-and-pepper patterns during various developmental processes. The proneural wave accompanies Notch activity that is propagated without the formation of a salt-and-pepper pattern. However, mathematical modelling and genetic analysis clearly demonstrated that Notch-mediated lateral inhibition is implemented within the proneural wave. Because partial reduction in EGF signalling causes the formation of salt-and-pepper pattern, it is most likely that EGF diffusion cancels salt-and-pepper pattern formation *in silico* and *in vivo*. Moreover, the combination of Notch-mediated lateral inhibition and EGF-mediated reaction diffusion enables a novel function of Notch signalling that regulates propagation of the wave of differentiation.

In our previous results, Notch signalling is activated only once at the wave front. However, Notch signalling is actually activated again behind the wave front forming twin peaks *in vivo*. The results of our parameter search show that the twin peaks of Notch activity can be reproduced by elevating the coefficient of cis-inhibition, by which Notch activity is autonomously repressed by Delta ligand. Moreover, the formation of the twin peaks could be stabilized by introducing strong non-linearity to cis-inhibition. The result of our *in vivo* experiment is consistent with the non-linear behaviour of cis-inhibition. The possible molecular mechanisms of non-linearity in cis-inhibition will be discussed.

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A mathematical model of planar cell polarity

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Many cells within epithelial tissues display polarity along a particular axis. This axis is perpendicular to the tissue plane and apico-basal axis (from top to bottom of tissues) of the cell. This phenomenon is called “planar cell polarity, PCP”, and is a common phenomenon found in many multicellular organisms. For example, hair cells in the inner ear of humans have many hairs on each individual cell, and since the hairs are regularly arranged on the cell plane, we can hear the sound. Not only hair cells, but fish scales, and body hair on mammals and the wings of birds etc., have cell polarity. As a result, these creatures carry out macroscopic morphogenesis.

Recently, since molecular biological research has developed concerning PCP, detailed molecular mechanisms have been revealed, several report is published [1-4]. On the other hand, major problems remain. In particular, 1. Mechanisms of morphogenesis for macro-level (PCP) and micro-level (molecular) information and 2. in considering PCP, what are the most important factors?

In order to solve these problems, we construct a simple mathematical model for PCP [5]. This model is based on the molecular mechanisms of PCP. In this talk, we will introduce our mathematical model and simulation result. Despite of our model is very simple formulation, it can reproduce various aspects of the PCP. From the view point of our mathematical model, let's think “What is the most important mechanism in PCP”.

[1] Jean-François Le Garrec *et al.*, *Developmental Dynamics* 235:235-246. (2006)

[2] Yoram Burak *et al.*, *PLoS Computational Biology* Vol 5(12), e1000628. (2009)

[3] Benoît Aigouy *et al.*, *Cell*, 142, 773-786, September 3. (2010)

[4] K. Amonlirdviman *et al.*, *Science* Vol 307, 423-426. (2005)

[5] Ayukawa,T., Masakazu, A. *et al.*, *Cell Reports*, 8(2): p. 610 - 621, 2014.

Cellular & tissue processes / 426

Mathematical model of contractile ring-driven cytokinesis in a three-dimensional domain

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In this presentation, a mathematical model of contractile ring-driven cytokinesis is presented by using both phase-field and immersed-boundary methods in a three-dimensional domain. It is one of the powerful hypotheses that cytokinesis happens driven by the contractile ring; however, there are only few mathematical models following the hypothesis, to the author's knowledge. I consider a hybrid method to model the phenomenon. First, a cell membrane is represented by a zero-contour of a phase-field implicitly because of its topological change. Otherwise, immersed-boundary particles represent a contractile ring explicitly based on the author's previous work. Here, the multi-component (or vector-valued) phase-field equation is considered to avoid the emerging of each cell membrane right after their divisions. Using a convex splitting scheme, the governing equation of the phase-field method has unique solvability. The numerical convergence of contractile ring to cell membrane is proved. Several numerical simulations are performed to validate the proposed model.

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Mathematical modelling for autophagosome formation

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Autophagy is an intracellular degradation process mediated by the autophagosome. The membrane dynamics of autophagosome formation is unique and complicated, which involves development of a small membrane cisterna into a cup-shaped structure and a double membrane spherical structure by closing the edge [1].

In this presentation, we discuss the mechanism of autophagosome formation from a physical point of view. A flat cisterna has a highly-curved rim, which is energetically unstable. As increasing the membrane surface, the rim area also increases. In order to reduce the energy, the cisterna is spontaneously curled by decreasing the rim area. Accordingly, a shape transition occurs suddenly due to the first order transition [2].

However, live-imaging experiments have shown that autophagosome formation takes place gradually and sudden closure of a flat membrane is not observed. We hypothesize the presence of protein(s) that stabilize the highly-curved rim, which enables gradual enclosure. Indeed, several autophagy proteins are present at the rim.

Thus, we consider the effects of the rim-stabilizing proteins on the dynamics of autophagosome formation. We show that the proteins localize at the highly-curved rim and stabilize it. As a result, intermediate cup-shape states appear and the closing dynamics becomes moderate similar to that of autophagosome formation *in vivo*.

[1] Mizushima 2017, PMID28186333

[2] Knorr *et al.*, 2012, PMID22427874

Cellular & tissue processes / 191

Growth-induced buckling in elastic rods

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Mechanically-induced buckling underlies the shape and function of a number of biological processes, such as brain tissue folding, intestinal crypt fission, and seashell formation. Unlike many typical engineering systems in which buckling is induced by an external compressive load, mechanical instability in biology is driven often by internal growth. In these contexts, it is just as important to consider how the system evolves beyond the onset of instability, as it is to understand when the instability occurs initially.

In this talk, we consider a growing, planar, elastic rod supported by an elastic foundation, as an appropriate starting point a number of possible biological systems. We analyse the post-buckling behaviour through a combination of weakly nonlinear analysis and numerical methods. The effect of different material parameters on the type of buckling and the buckled shape is shown. We then examine how spatial heterogeneity in substrate adhesion, elastic rod stiffness, and growth, impacts both the instability and resultant post-buckled shape evolution. These heterogeneities are contrasted with heterogeneity within the foundation shape, echoing classical results by Koiter on imperfection sensitivity and failure [1]. Finally, we discuss extensions that specialise the model to that of a buckling intestinal crypt.

[1] Van der Heijden, Arnold MA, ed. WT Koiter's elastic stability of solids and structures. Cambridge: Cambridge University Press, 2008.

Cellular & tissue processes / 510

Temporal dynamics of macrophages plasticity in the bone microenvironment

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Tumour associated macrophages have long been implicated in the progression of primary solid malignancies including prostate cancer. Metastatic prostate cancer typically manifests in the bone where it induces painful osteogenic lesions that are incurable. Bone is naturally rich in myeloid derived macrophages whose temporal polarization into pro- (M1) and anti-inflammatory (M2) phenotypes is critical for regulating the program of bone injury repair mediated by bone resorbing osteoclasts (OCL) and bone building (OBLs). However, the dynamics of macrophage polarization in the context of bone metastatic prostate cancer is underexplored and difficult to address with traditional biological approaches. In order to address it we built a mathematical model describing bone resident cell population dynamics during bone injury response through a set of coupled ordinary differential equation (ODE). We informed this model by analyzing macrophage plasticity *in vivo* subsequent to intratibial injury. Bone marrows were isolated at several time points and profiled by flow cytometry for pro- and anti-inflammatory macrophage content. Contralateral tibias were analyzed for bone volume, osteoblast and osteoclast numbers. The ODE model was able to predict experimental observations of M1/M2, OBL, OCL and bone dynamics. Generation of the ODE model required testing a number of assumptions regarding macrophage polarization behaviour. For example, it is unknown whether M1 resolve at the initial stages of bone injury repair through death, or by re-polarizing into M2. For each aspect, competing mechanistic assumptions were proposed and simulated mathematically by sets of ODEs. The best fitting assumptions for each aspect were integrated into a comprehensive ODE model to fully describe the dynamics of the bone resident cell populations during bone repair. This experimentally validated model is now being exploited to address how bone population dynamics respond to metastatic prostate cancer cells and subsequently identify the resultant impact on bone formation and cancer growth.

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Insights from including the microtubule cytoskeleton in modelling mRNA localization

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The cellular cytoskeleton ensures the dynamic transport, localization and anchoring of various proteins and vesicles. In the development of egg cells into embryos, messenger RNA (mRNA) is transported along microtubule filaments and must accumulate at the cortex of the egg cell on a certain time and spatial scale. We present two equivalent methods of deriving the effective transport properties of mRNA at large time: using analysis of partial differential equations, and using renewal rewards processes in a stochastic model formulation. The dynamical systems model approach can be extended to include the geometry of the microtubule filaments. This allows us to better predict the spread of the particles, and to investigate the contribution of an anchoring mechanism to the timescale of localization. Our numerical studies using model microtubule structures predict that anchoring of mRNA-molecular motor complexes may be most effective in keeping mRNA localized near the cortex and therefore in healthy development of oocytes into embryos.

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Quantifying the influence of nanoparticle polydispersity on cellular delivered dose

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Nanoparticles provide a promising approach for the targeted delivery of therapeutic, diagnostic and imaging agents in the body. However, it is not yet fully understood how the physicochemical properties of the nanoparticles influence cellular association and uptake. Cellular association experiments are routinely performed in an effort to determine how nanoparticle properties impact the rate of nanoparticle-cell association. To compare experiments in a meaningful manner, the association data must be normalised by the amount of nanoparticles that arrive at the cells, a measure referred to as the delivered dose. The delivered dose is calculated from a model of nanoparticle transport through fluid. A standard assumption is that all nanoparticles within the population are monodisperse, namely, the nanoparticles have the same physicochemical properties. We present a semi-analytic solution to a modified model of nanoparticle transport that allows for the nanoparticle population to be polydisperse. This solution allows us to efficiently analyse the influence of polydispersity on the delivered dose. Combining characterisation data obtained from a range of commonly-used nanoparticles and our model, we find that the delivered dose changes by more than a factor of two if realistic amounts of polydispersity are considered.

Competition, coexistence, mutualism / 419

Quantifying the value of monitoring species in multi-species, multi-threat systems

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Making effective management decisions is challenging in multi-species, multi-threat systems because of uncertainty about the effects of different threats on different species. To inform management decisions, we often monitor species to detect spatial or temporal trends that can help us learn about threatening processes. However, which species to monitor and how to monitor to inform the management of threats can be difficult to determine. Value of information (VOI) analysis is an approach for quantifying the value of monitoring to inform management decisions. We developed a novel method that applies VOI analysis to quantify the benefits of different species monitoring strategies in multi-threat, multi-species systems. We applied the approach to compare the effectiveness of surveillance monitoring (monitoring species without experimentation) to targeted monitoring (monitoring species with experimentation to learn about a specific threat), and how prior information drives the benefits of these two different strategies and the species to monitor. We also illustrate the approach by applying it to two contrasting case studies for monitoring and managing declining mammals in Western Australia. Our approach shows that surveillance monitoring generally provides far lower benefits than targeted monitoring for managing threats in multi-species, multi-threat systems under economic constraints. Our approach also informs the choice of species to monitor and which threats to manage experimentally to most improve threat management outcomes. We show that the key parameters driving these choices include: the budget available for management, prior understanding of which threats cause declines in which species, the relative cost of managing these threats, and the background probability of decline. Our new VOI approach allows the evaluation of monitoring decisions in multi-species, multi-threat systems in the face of uncertainty, while explicitly accounting for the improvement in management outcomes. We recommend that managers need to explicitly consider a range of decision parameters when selecting which species to monitor to inform management. Our framework provides an objective way to do this.

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The complex effect of the evolutionary rates on generalized mutualistic communities

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Mutualism or cooperation between and among species is ubiquitous in nature. The most well-known examples of mutualism are Müllerian mimicry and division of labour. In Müllerian mimicry, unpalatable species have evolved the similar appearances and they are less likely to be predated upon because the predators effectively learn that these species are noxious. In division of labour, each species specializes in a special task, such as producing different nutrients.

Conflict can arise in mutualism regarding the roles of each species. In Müllerian mimicry, it could be more advantageous to be a model species than a mimic because the life cycles, the habitats, and the body plans of model species are innate. In division of labour, conflict can arise regarding species tasks; when producing nutrient, one type of nutrient might have a greater cost for the organism than another type of nutrient.

The effect of evolutionary rates on mutualistic symbioses with a degree of conflict has been conceptualized using the snowdrift game. Bergstrom and Lachmann (2003) [1] have found that in a model of the mutualistic symbiosis between two species, the slower evolution can be favoured. This effect

was named Red King effect, which is converse to Red Queen effect, where the faster evolution is favoured mainly in, but not restricted in, antagonistic symbioses.

Mutualism, however, can involve more than two species. In the context of the mimicry, such phenomenon is known as the Müllerian mimicry ring. Mutual symbioses with division of labour are not always limited in one-to-one relationship. For example, green algae can display mutualism with several phylogenetically broad fungal species.

In this study, the original model in Bergstrom and Lachmann (2003) was expanded by generalizing the number of species M ($M \geq 2$) in a community. In this model, Red Queen effect can shift to Red King effect and vice versa over time. For example, when $M = 3$, Red Queen effect can remain until one species (in many cases, the fastest-evolving species) fixes its strategy, after which Red King effect comes into play and the slowest-evolving species is favoured. As a result, the fastest- and slowest-evolving species exploit the remaining species.

This result suggests the complexity of the effect of evolutionary rates on mutualistic coevolution. Even when differences in evolutionary rates of two species are determined, predicting which species is more likely to exploit the other is challenging, because a third species with which both species mutually interact could also have an evolutionary effect on the other two species.

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Competition, coexistence, mutualism / 184

Evolution and maintenance of mutualism between tubeworms and sulfur-oxidizing bacteria

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Tubeworms and sulfur-oxidizing bacteria mutualism, an essential part of the chemosynthetic ecosystem in the deep-sea, has several puzzling features. After acquiring sulfur-oxidizing bacteria from the environment, tubeworms become fully dependent on their symbiont bacteria for nutrient intake. Once ingested by the tubeworm larva, no additional symbionts join from the environment, and no symbionts are released until the host tapeworm dies. Despite this very narrow window for symbionts, some tubeworm species can live for >200 years. Such a restricted release of symbionts could lead to a shortage of symbiont bacteria in the environment without which tubeworms could not survive. In our study, we examine the conditions under which this mutualism can persist, and whether the host mortality evolves toward a low value, using a mathematical model for the tubeworm-symbiont bacteria system. Our model reveals that mutualism can persist only when host mortality is within an intermediate range. Moreover, with weak competition among symbionts and their slow growth within a host, host mortality evolves toward a low value, without driving either host or symbiont to extinction. We also found the parameter conditions that lead to the unlimited evolutionary escalation of host mortality toward extinction of both tubeworms and symbionts populations (evolutionary suicide).

Data-driven mechanistic cancer models / 356

Modelling brain tumour recurrence patterns following surgical resection with ischemia

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Glioblastoma Multiforme (GBM) is the most aggressive primary brain tumour, with a median life expectancy of only 15 months with treatment. Although surgical resection is a standard-of-care procedure, the migratory nature of the tumour cells limits its efficacy as not all tumour cells can be removed. The tumour will usually re-establish itself along the resection cavity wall, known as a local recurrence, but it can recur elsewhere or become more migratory, known as a distal recurrence. Clinical data has shown that patients with ischemia following resection are more likely to have a distally recurring tumour, with an incidence rate of 61% for those with ischemia vs 19% for those without. This evidence suggests that a lack of nutrients plays a role in the tumour recurrence pattern but does not fully answer the question regarding the difference between tumours that do or do not recur distally under these conditions.

We present the Proliferation Invasion Hypoxia Necrosis Angiogenesis (PIHNA) model that simulates the angiogenic cascade of a GBM as it grows. We have applied this mechanistic model to show how an in silico GBM grows following resection and subsequent ischemia, and to highlight the role of the individual tumour kinetics in this behaviour. Our simulations suggest that the diffusivity of the tumour, the tumour cell proliferation rate, and the hardness of the cells all play key roles in the recurrence location of a GBM.

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Modelling growth and treatment dynamics in PDGF-driven glioblastoma: how heterogeneity manifests across scales

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Glioblastoma multiforme (GBM) is a rare brain cancer with a median survival of only around 15 months. Intratumoural heterogeneity and extensive infiltration into the brain tissue contribute to poor prognosis and probable recurrence. Predicting the timing of post-treatment recurrence is often limited if using only MRI imaging measurements, as a diverse range of treatment outcomes can result from similar pre-treatment growth dynamics. To better understand the diversity in recurrence, we analyze multiscale data from an ex vivo rat model during progression to inform an agent-based computational model to quantify how heterogeneity in proliferation and invasion affects both the bulk and individual scale tumour metrics following treatment.

The rat experiment is a model of platelet-derived growth factor (PDGF) driven GBM. The production of PDGF by cells allows both autocrine and paracrine stimulated proliferation and migration to drive growth. PDGF in the tissue environment also stimulates and recruits normal progenitor cells. Throughout this experiment, bulk tumour size was recorded via MRI, and single cell tracks were

analyzed to quantify proliferation and migration spatially. Guided by this data, we built an agent-based model within the gray-white brain tissue context. We fit the model to the growth data alone using a hybrid genetic algorithm approach, and then fit individual cell proliferation and migration distributions.

We find parameter sets that define a suite of fits, which describe similar bulk scale growth dynamics with widely different underlying phenotypes that tend to be more proliferative, more migratory, or more driven by growth-factor dynamics. A more limited set of parameters fits the individual scale dynamics, with heterogeneity predicted to be both an intrinsic feature and driven by the environment. Application of an anti-proliferative treatment on these heterogeneous tumours reduces tumour size, but leads to recurrence of a less proliferative tumour. An anti-migratory treatment is seen to have little effect on growth dynamics, but selects for more proliferative phenotypes. The changes that occur at the imaging scale down to the single cell level lead to a better understanding how the evolutionary impact of treatment on GBM can inform treatment regimens.

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Multiscale modelling accurately predicts *in vivo* response of combined IL-6 blockade and traditional chemotherapy in stem cell driven cancers

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It is well known that growth and survival of cancer stem cells (CSCs) is highly influenced by tumour microenvironmental factors and molecular signalling, initiated by cytokines and growth factors. IL-6 is a key regulator of a number of cellular processes including proliferation, survival, differentiation, migration and invasion and it is also commonly overexpressed in many cancers. Recent evidence shows that IL-6 is not only secreted by tumour cells, but is produced at even higher levels by endothelial cells (ECs). Research shows that high intratumoural levels of IL-6 enhance the survival, self-renewal and tumour initiation potential of cancer stem cells. These studies of the impact of IL-6 on CSCs provide strong motivation for the development of anti-IL-6 therapies for the targeted treatment of stem cell driven cancers.

In this talk, a multi-scale mathematical model that operates at the intracellular, molecular, and tissue level is developed in order to investigate the impacts of endothelial cell-secreted IL-6 signalling on the crosstalk between tumour cells and ECs during tumour growth. This endothelial cell-tumour cell (EC-TC) model is used to study the therapeutic impact of Tocilizumab (TCZ), a competitive IL-6R inhibitor, on tumour growth and cancer stem cell (CSC) fraction, alone and in combination with the traditional chemotherapeutic agent, Cisplatin. The approach used here is novel in that it includes full receptor occupancy dynamics between endothelial-cell produced IL-6, IL-6R, and TCZ. Validation is achieved by directly comparing model predictions to data generated by a series of *in vivo* experiments. This multiscale approach provided excellent predictive agreement with the decrease in tumour volumes, as well as a decrease in CSC fraction.

Targeting key regulators of the cancer stem cell phenotype to overcome their critical influence on tumour growth is a promising new strategy for cancer treatment. This predictive modelling framework can serve to rapidly evaluate dosing strategies for IL-6 pathway modulation, as well as providing the basis for proposing combination treatments with IL-6 blockade and cytotoxic or other targeted therapies.

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Optimal cancer screening regimes in gastrointestinal evolution using mathematical modelling

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Mathematical modelling of the stochastic evolutionary process of carcinogenesis can be used to derive and to optimize the timing of clinical screens so that the probability is maximal that an individual is screened within a certain “window of opportunity” for intervention when early cancer development may be observed. By using data from epidemiological studies with long-term patient follow-up, empirical approaches aid in screening design and may inform cost-effectiveness analyses to compare proposed screening and intervention strategies. However, mechanistic modelling that incorporates a greater level of biological understanding and detail for how and when normal tissues progress to cancer can be used for a more refined screening design than typically implemented in population screening studies. With examples in inflammation-driven premalignant disease of the gastrointestinal tract, I will introduce calibrated multistage clonal expansion models of carcinogenesis, derive probability equations used for optimal screening times and risk estimation, and present results for screening strategies using inferred parameters from US cancer incidence data. These results 1) provide a robust statistical framework for quantifying when it is optimal to screen and begin surveillance for premalignant changes, and 2) are shown to be cost-effective in Barrett’s esophagus patients, particularly with increasingly sensitive and minimally invasive sampling procedures used in clinical practice.

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Glioblastoma invasiveness may predict response to therapies with high or low blood brain barrier penetrability

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Introduction: Glioblastoma (GBM) is a very aggressive primary brain cancer, noted for its diffuse infiltration into surrounding normal-appearing brain. This particular nature makes GBM notoriously difficult to treat, as these diffusely invading cells cannot be resected surgically, are difficult to target with radiation therapy, and thus must be targeted with chemotherapy. However, this too presents a challenge, as these invading GBM cells reside beyond the dense tumour regions where angiogenesis causes disruption of the blood brain barrier (BBB) and allows drugs to more readily enter the central portion of the tumour. Thus, it is critical to determine predictors of drug distribution in individual patients’ tumours and surrounding brain tissue to ensure the invading GBM cells are exposed to the therapy.

Objective: Determine predictors of drug distribution and effect from non-invasive imaging using minimal mathematical approaches.

Methods: Following experiments treating murine orthotopic patient-derived xenografts (PDXs) of GBM with various anti-tumour therapies, we compiled data from both the xenografts and the original patients from which the PDX lines were derived. This data included bioluminescence imaging (BLI), lamin-stained histological sections, and magnetic resonance imaging (MRI) from the PDXs, as well as patient MRIs and clinical data. Using the time series BLI data from PDXs, we developed and parameterized minimal differential equation models of PDX tumour growth for individual PDX lines, adjusted for lead time bias using a nonlinear mixed effects approach. This gave us an overall growth rate for each of the PDX lines across multiple subjects. Next, we compared these growth and invasion characteristics with therapeutic response in patients and PDX subjects to agents with different CSF to plasma ratios, indicating the degree of blood brain barrier penetrability of these drugs.

Results: Individual PDX lines have different growth kinetics, and recapitulate the kinetics observed in the original patients from which the lines are derived. Further, these growth kinetics appear to be correlated with differential drug response, with more diffusely infiltrating tumours responding better to drugs with higher CSF to plasma ratios.

Conclusion: While further work is needed to verify our results across more PDX lines, our results suggest that noninvasive imaging-based characterization of tumour invasiveness may be able to aid in matching patients to the best therapy for their individual tumours.

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The coexistence and its sustainability in Batesian mimicry

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Batesian mimicry is a common phenomenon in nature, and it has been reported in various taxa. In Batesian mimicry, there are two species that have a similar colouration. One species is toxic or unpalatable, we call it “model-species”. The other is nontoxic or palatable, we call it “mimic”.

While many mathematical models focused on the evolution of mimicry, only a few mathematical models focused on community dynamics. Furthermore, the sustainability of the coexistence has not been studied. Here, we addressed the community dynamics and its sustainability in this study.

A part of the previous mathematical models has a common framework based on simple and plausible assumptions such as density-dependent effect and frequency-dependent predation. However, even a simple mathematical model based on the framework has not been analyzed completely. The simple mathematical model is also important mathematically because it is one of the basic models that have both density- and frequency-dependent effects and actually it includes a ratio-dependent predator-prey model.

The objective of our study is as follows; first, to solve a mathematical model based on the common framework completely and understand its properties. Secondly, to examine the impact of mimicry on community dynamics. Thirdly, to discuss the sustainable coexistence of model-species and mimic.

We focused on the case that the intrinsic growth rate of model-species is less than mimic because model-species pay some cost for acquiring toxicity and defined “predation impact (PI)” as the predation rate divided by the intrinsic growth rate. The result is divided into two types using PIs of model-species and mimic species; type I is when the predation impact of model-species is small, type II is when the predation impact of model-species is large. In type I, model-species and mimic always coexist. In type II, they can coexist, but not always. In particular, in type II, when the ratio of the carrying capacity change and become less than a threshold, model-species become extinct. Thus,

the coexistence of model-species and mimic is unlikely to be maintained in type II under a varying environment. Therefore, Batesian mimicry in nature is supposed to be maintained in type I.

In our mathematical model, there are only three stable states; coexistence, mimic alone and both extinction. This result can explain the geographic distribution of model-species and mimic in more than 10 mimicry systems. For example, eastern coral snake is a toxic model and scarlet kingsnake is a nontoxic mimic in North America. In their geographic distribution, the areas of coexistence, mimic alone and both-absence were observed with latitude gradient. This pattern of the geographic distribution is consistent with the result of our mathematical model.

In addition to the above study, we construct some models, taking predator's learning process into account. We present the results derived from these models and compare them.

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The importance of immigration over niche effects in maintaining island biodiversity

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In recent times, unprecedented rates of biodiversity loss have resulted in a pressing need for greater understanding of key processes maintaining biodiversity. These processes are often studied in island communities because they exhibit low complexity relative to their mainland counterparts, which helps to simplify experiments, data analyses and mathematical models. Much previous work on islands has focused on local processes such as competition and predation, but this neglects processes operating at broader, regional scales. In particular, immigration can carry individuals of new species into a local area, and can therefore play a pivotal role in maintaining biodiversity.

The importance of immigration was recognized half a century ago by the seminal Theory of Island Biogeography, which postulated that the number of species on an island results from a dynamic balance between immigration and extinction. However, the theory did not explicitly consider the simultaneous effects of local and regional processes on the abundance dynamics of species populations in island communities, and hence did not predict which type of process was the dominant driver of island biodiversity.

In our work, we addressed the key knowledge gap identified by quantifying the relative influence of local and regional processes on species richness of islands, using a suite of dynamic models. Each model represents species populations competing for common resources on an island, with immigration from a mainland source; however, the details of interspecific competition differ among models. The models include the classic Lotka-Volterra model and Tilman's model of resource competition.

We found that for all models examined, the equilibrium number of species was typically low when immigration intensity was low, regardless of the level of competition. In this "niche-structured" phase, species dynamics were governed by deterministic competition, with typically a few species coexisting per available niche. However, as the immigration intensity increased beyond a threshold, the number of species exhibited a rapid increase. In this "immigration-structured" phase, species dynamics were governed by stochastic immigration, which allowed many species to coexist per available niche. These trends in species richness were consistent with data from empirical datasets for 100 archipelagoes worldwide, covering five taxonomic groups and three archipelago types. Our results highlight the general importance of maintaining immigration to achieve high levels of island biodiversity, which is directly relevant to conservation and sustainable management.

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Host- vs diet-derived nutrient balance, and carbon vs nitrogen limitation, determines the effect of dietary intervention on the microbiome.

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The gut microbiome is implicated in a growing array of diseases, spanning asthma, allergies, obesity and autoimmunity. The need for interventions that return aberrant dysbiotic communities to symbiotic partners is clear. Yet, despite known sensitivities to diet, a conceptual framework through which to design rational interventions remains elusive.

We adopted an ecological perspective in building a conceptual model to reason about how diet impacts the microbiome. Microbes must satisfy their nutritional requirements for life. The most readily limiting resources are carbon, as an energy source, and nitrogen, a key element in all amino acids.

Microbes employ a diversity of strategies to satisfy these nutritional requirements. Some specialise on metabolising diet-derived substrates such as fibre. Others can grow on mucin, a host secretion, alone. We further envisage hybrid strategies between these two extremes, where carbon and nitrogen substrates either both originate from the diet or the host, or one from each.

We evaluated this ecological conceptualisation's capacity to explain observed microbiome responses to diet through the construction of an agent-based model. Host mucin secretion and dietary nutrient absorption dynamics have been estimated from literature, the remaining dietary nutrients being supplied to a one dimensional simulated gut environment that houses bacteria. Each bacteria cell agent internalises nutrients from its local environment, targeting a 5.2:1 carbon:nitrogen ratio. Nutrient-rich cells exhibit a higher probability of division, where nutrient-poor cells likely perish.

Our modelling work was closely aligned with an *in vivo* murine dietary study. Herein, 112 mice were administered diets systematically varying in protein:carbohydrate:fat distribution, and energy density by diluting these mouse-accessible nutrients with cellulose, which neither mouse nor its microbiome can metabolise. Their actual intake, and hence the energy they derive from each macronutrient, was recorded. Using generalised additive models we interpolated from these 112 samples across a wide dietary intake space. As such, we could ascertain how each microbe responds to a given diet. We observed two broad patterns of response: microbes that thrive under energy-rich or energy-poor diets. The dietary intakes of each of these 112 mice were simulated in our model, which broadly recapitulated these *in vivo* observations. This suggests that the balance of host- versus diet-derived substrates is a critical factor in shaping the microbiome.

Our model permits a comprehensive exploration of how multiple dietary factors, such as prebiotic administration, fasting regimes, macronutrient distribution and energy density, interact in impacting the microbiome. The model predicts that interventions such as fasting and prebiotic (fibre) administration do not have uniform effects, which, rather, depend on other dietary parameters also. For instance, prebiotic administration in low-protein diets can have a limited effect, as under these diets microbes are nitrogen-limited, and the carbon prebiotics supply is of little consequence. These results underscore the importance of taking an integrative approach to studying diet-host-microbiome interactions, and tools such as these offer a promising path to designing personalised dietary interventions to rationally manipulate a person's microbiome.

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Ecotoxicological dynamics subject to stoichiometric constraints

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The development of ecotoxicological models over the last couple decades has significantly contributed to interpreting how contaminants impact organisms and cycle through food webs. However, there is increasing evidence that organisms experience interactive effects of contaminant stressors and food conditions, such as resource stoichiometry and nutrient availability. *Stoichiometric Ecotoxicology* modelling efforts shed light on nutrient and chemical contaminant cycling and ultimately can help improve toxicological risk assessment protocols. We are formulating a series of empirically testable and robust models of algae-*Daphnia* population dynamics subject to concurrent nutritional and contaminant stressors. In parallel to developing the models, we are conducting laboratory experiments manipulating the nutritional content of algae fed to *Daphnia* exposed to Cadmium, Arsenic, and Copper. Here, we present modelling and empirical results and discuss the synthesis of the two approaches.

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To remain in the natal stream or migrate to the ocean-density-dependent growth of juvenile salmonids could lead to fluctuating populations and evolutionary bistability

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Male juveniles of several species of salmonids spawning in fresh water streams migrate to the ocean and return to their natal stream when they mature (migratory tactic); others stay and mature in the stream (resident tactic). Large individuals become residents and small ones become migrants. This is an evolutionary outcome according to the status-dependent strategy model, which assumes that the juveniles exhibit the optimal tactic based on their status. In this study, we consider the case in which the density of adult residents suppresses juvenile growth, and explore the dynamics of alternative tactics and the evolution of threshold size. We show that a fraction of the migratory tactic that might converge into a stable state or continue to fluctuate wildly, and that the evolutionary outcome may be evolutionarily bistable, resulting in a clearly different threshold size. In the case of evolutionary bistability, two threshold sizes differ in ecological dynamics: a stable fraction of migratory tactic in one and two-year periodic fluctuation in the other.

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Adaptive partner recruitment by hosts can help maintain a diversity in mutualistic systems

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Mutualisms are reciprocally beneficial interactions between heterospecific organisms. Theoretical studies have predicted that genetic diversity in mutualistic systems should decrease over time because of innate positive feedback structure of the interaction. Negative feedback due to asymmetry in the exchange of benefits can maintain the diversity and stabilize multi-strain mutualistic systems, but partner preference for more beneficial partners might reduce such asymmetry and strengthen the positive feedback. Here I develop a replicator dynamics model for a mutualistic system between two host and two symbiont strains to clarify conditions that can stabilize multi-strain mutualisms in which the positive interspecies feedback is dominant. I assume that one symbiont strain is mutualistic for one host strain but parasitic for the other, whereas the other symbiont strain is the opposite. Hosts choose multiple symbiont individuals from the environment and discriminately offer them resources (e.g. photosynthates in legume–rhizobium mutualisms), and only mutualistic symbionts spend a fraction of the resources on producing beneficial products for their hosts (e.g. nitrogen fixation by rhizobium). The fitness of a host is proportional to the product of the amount of remaining resources and that of receiving beneficial products, while the fitness of a symbiont is proportional to the amount of the rest of resources offered by its host. I assume that proportions of resources to spend for hosts are different between the two symbionts, and values of other parameters including the partner preference are identical between the two mutualistic associations of the hosts and symbionts.

I show that two host and symbiont strains can coexist stably under strong partner preference by hosts if hosts adaptively adjust the number of associating symbionts, even when the intra-strain competition among hosts is not strong enough for coexistence of the strains by itself. They can also coexist under weak partner preference. However, under moderate partner preference the coexistent equilibrium is dissolved and the strains cannot coexist.

Education / 135

Strong inference in mathematical modelling: a new twist to an old idea

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While there are many opinions on what mathematical modelling in biology is, in essence, modelling is a mathematical tool which allows consequences to logically follow from a set of assumptions. Only when this tool is applied appropriately, it may allow to understand importance of specific mechanisms/assumptions in biological processes. Mathematical modelling can be less useful or even misleading if used inappropriately, for example, by creating a false impression of a good understanding of biological processes. It has been argued that the best use of mathematical models is not when a model is used to confirm a hypothesis but rather when a study shows inconsistency of the model (defined by a specific set of assumptions) and data. Following the principle of strong inference for experimental sciences proposed by Platt, I suggest “strong inference in mathematical modelling” as an effective and robust way of using mathematical modelling to understand mechanisms driving dynamics of biological systems. The major steps of strong inference in mathematical modelling are 1) to develop multiple alternative models for the phenomenon in question; 2) to compare the models with available experimental data and to determine which of the models are not consistent with the data; 3) to determine reasons why rejected models failed to explain the data, and 4) to suggest experiments which would allow to discriminate between remaining alternative models. The use of strong inference is likely to provide better robustness of predictions of mathematical models and it should be strongly encouraged in mathematical modelling-based publications in the 21st century.

Education / 27

Quantitative modelling by biology undergraduate students

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Quantitative Undergraduate Biology Education and Synthesis (QUBES) is an NSF funded project with the mission to improve learning opportunities for all students enrolled in undergraduate biology courses by reflecting the centrality of quantitative approaches in modern biology. We will provide an overview of the QUBES project, then discuss the Quantitative Modelling assessment QM BUGS. The diagnostic assessment and associated RTOP observation protocol have been administered in biology classes at two universities. The assessment consists of 30 questions on quantitative modelling ability and student confidence about modelling. We will report the findings from a pilot administration in Fall 2017 and discuss revision of the assessment informed by Rasch Analysis.

Education Subgroup Lunch and Panel on Assessment of Interdisciplinary Thinking / 141

SMB Education Subgroup Business Meeting Lunch and Panel on Assessment of Interdisciplinary Thinking

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Carrie Diaz Eaton, *Moderator and Education Subgroup Chair, Bates College, USA*

As higher education moves towards evidence-based curriculum reform, assessing interdisciplinary thinking becomes a challenge for those in multidisciplinary frontiers. We will discuss how to best support SMB Education subgroup members. We will also introduce some resources for assessing interdisciplinary thinking in your courses.

Robert Mayes, *Georgia Southern University, USA*

The QM BUGS assessment measures students' proficiency in quantitative modelling (QM - ability to develop a model). The assessment is intended to be given in undergraduate biology courses where quantitative skills are preparing students or actively engaging students in quantitative modelling within biological contexts. Assessment consists of 30 questions: 19 multiple choice questions (5 options) addressing quantitative modelling understanding and 11 Lickert questions (1 NA, 2 Strong Disagree to 5 Strongly Agree) addressing student confidence about modelling in biology.

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The underlying goal of this project is to develop and evaluate an interdisciplinary instrument—a Biology Calculus Concept Inventory (BCCI)—which will allow assessment of calculus concept learning goals in the context of concrete, real-world life science data examples and models.

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A numerical simulation of an edge-based SEIR model on random networks

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Networks representing the spread of infectious diseases in populations have been widely studied. Here, we formulate an SEIR model using an edge-based approach on a static random network with arbitrary degree distribution. The corresponding basic reproduction number and final epidemic size are computed. The SEIR model is used to investigate the stochasticity of the SEIR dynamics. Assuming exposed, infection and recovery each happen at constant rates, stochastic simulations of the SEIR dynamics are performed applying continuous-time Gillespie's algorithm given a Poisson or a power law with exponential cut-off degree distributions. The resulting simulations match well with the numerical predictions of the SEIR model given the initial conditions. Final epidemic size remains unchanged when the initial infecteds are varied. On the other hand, varying the disease parameters of the SEIR model affects the time when the epidemic accelerates, the peak of the epidemic, and the final epidemic size. These results capture scenarios of an epidemic in a network implying control strategies in the disease transmissions.

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Spatial and temporal analysis of FluTracking data and implications for influenza spread in Australia

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Modelling the spread of influenza across Australia is of substantial public health concern. However, there are many challenges in creating accurate models, including how best to capture the spatial and temporal characteristics of the disease spreading process, and aligning with the actual contact process and mobility of individuals in the population. How influenza spreads spatially, whether by infecting neighbouring regions or through major domestic centres via air traffic, is of particular interest in building predictive models. Recent work has suggested the spread of influenza in the United States is dominated by work commutes rather than air traffic. In contrast, influenza in Australia has been shown to have highly synchronized epidemics between major cities across large geographic distances and varying climates.

FluTracking is a participatory online health surveillance system for monitoring influenza-like-illness (ILI), with one of its principal aims to detect the onset of influenza in Australia. Since 2010, there are over 10,000 participants each year, with participation continuing to increase. In this work, we analyse weekly reports from the FluTracking system from May 2011 to October 2017 to infer spatial and temporal dynamics of influenza in Australia. These dynamics could then be used as a starting point for building contact and contagion networks in models for epidemic forecasting, and lead to a greater understanding of the mechanisms behind the spread of influenza-like-illness in Australia.

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An age-dependent mathematical model and vaccination strategies for 2009 A/H1N1 influenza in the Republic of Korea

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In this talk, we will present a mathematical model of 2009 A/H1N1 influenza considering age structure in the Republic of Korea and suggest vaccination strategies for mitigating the epidemics. There were 750,000 confirmed cases of 2009 A/H1N1 influenza from May 2009 and August 2010. Because influenza viruses are spread through close contact, contact pattern plays an important role for the disease spread. We developed an age-dependent SEIAR model. The total population is divided into five subgroups and age-specific transmission rates are estimated based on laboratory confirmed data from Korea Centers for Disease Control and Prevention (KCDC). Vaccination policies is important to minimize the number of infected individuals especially when the vaccine supply is limited. Using mathematical model, we could assess the impact of the age-dependent vaccination priority on transmission dynamics.

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Individually based stochastic model of influenza: an analysis of school closure

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In this research, we proposed an infectious disease spread model of influenza which was individually based and stochastic. We first described the method to build a realistic model, or to estimate realistic parameter values, based on observed data. An appropriate model has to be individually based and stochastic if we take advantage of small unit data (in this case, every day class unit data). We also analysed the effect of different strategies of school closure, e.g., the criteria for implementing school closure and the duration of continuous school closure.

The data we used were the daily reported data of the numbers of cases of swine flu and the dates of school/class closure in each class of schools collected from September 2009 to March 2010 in a city in Japan. Because the data were collected in each class, transmission rates could be estimated separately for within class, within-school and inter-school rates. Totally 21,253 cases were reported out of 51,871 students in 134 schools (elementary schools, junior high schools, high schools and kindergartens). To construct accurate model, infected numbers must be estimated from case report data taking latent period into account, which is deterministically impossible. To resolve this difficulty, we stochastically estimated and obtained data of infected numbers by 'Monte Carlo back calculation' and used in the analysis. The analysis was mainly carried out using data during September up to December to avoid the influence of vacations. The influence of humidity was also analysed using daily meteorological data of the area where data were collected. The analysis of total population using deterministic model was also carried out to obtain the overview of the flu spread.

The transmission rates of different levels were estimated by maximum likelihood method using detailed data reconstructed by Monte Carlo back calculation method. The rate within class was much larger (approximately 15 times larger) than within school rate. The transition rate between schools was much smaller than between classes of the same school. Stochastic variations of estimated parameters were also analysed. Optimal strategy of school closure was analysed in relation to the characteristics of flu.

By the analysis based on stochastic infectious disease spread model, we could have presented possible variations of total number of cases and the size and timing of the epidemic peak. 'Monte Carlo back calculation' approach was concluded to be useful in the analysis of effective preventive strategy against influenza based on individually based stochastic model.

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Understanding the impact of climate in seasonal influenza in Australia

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Influenza in humans exhibits a strong seasonal cycle in temperate climates, with a peak of varying intensity appearing each winter. However, the exact cause of this seasonal cycle remains poorly understood. We develop a climate-based SIR modelling framework to understand influenza seasonality, with the transmission rate as a function of climate data. By using a variety of climate-based functional forms of transmissibility from the literature, as well as some new forms, we select the best functional form for climate-dependent transmissibility via modern Machine Learning model selection methods. By analysing a unique dataset comprising ten years of GP-reported influenza-like-illness surveillance data from around Australia, we explore the relationship between influenza transmission and weather in different climate zones.

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Heterogeneity in susceptibility induces unpredictable outbreak

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Reinfection is known to induce complex epidemiological dynamics (e.g. sustained oscillation) due to the time-series change in susceptibility. The simplest model describing reinfection shows three epidemiological dynamics; disease-free, epidemic and endemic. These three dynamics can be classified by two reproduction numbers, basic reproduction number and reproduction number by only reinfection. However, the simplest model takes into account only two variations of susceptibility, susceptibility at first infection and second or later infection. To relax this assumption we construct a parsimonious model describing three susceptibilities, i) susceptibility at first infection, ii) partial protection at second or later infection and iii) perfect protection at second or later infection. This model demonstrates an interesting dynamics, outbreak occurs after the temporal decrease in the number of infected individuals. We named this dynamics as “delayed outbreak”. Basic reproduction number cannot capture outbreak potential of this dynamics. Our model is too simple to understand rich dynamics induced by heterogeneity in susceptibility, for example, endemic situation is not captured in this model. To understand the dynamics with heterogeneity in susceptibility, we expand our model to a model describing the transition of susceptibility by reinfection. We confirmed that “delayed outbreak” is robust if the heterogeneity in susceptibility against reinfection exists.

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Data-driven prediction and origin identification of epidemics in population networks

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While there exist a number of mathematical approaches to modelling the spread of disease on a network, analyzing such systems in the presence of uncertainty introduces significant complexity. In scenarios where system parameters must be inferred from limited observations, general approaches to uncertainty quantification can generate approximate distributions of the unknown parameters, but these methods often become computationally expensive if the underlying disease model is complex. In this talk, I will apply transitional Markov chain Monte Carlo (TMCMC) using a massively parallelizable Bayesian uncertainty quantification framework to a model of disease spreading on a network of communities, showing that the method accurately and tractably recovers system parameters and selects optimal models in this setting.

Epidemiology / 248

Evidence for history-dependence of influenza pandemic emergence

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Influenza A viruses have caused a number of global pandemics, the most recent being the H1N1 pandemic in 2009, resulting in considerable human mortality. Despite influenza pandemics being rare events, with it currently being nearly impossible to predict the next influenza emergence event, it may be the case that the virus itself provides us with outbreak signals that should prompt us to be more prepared. Specifically, knowing whether or not influenza pandemic occurrences are uniformly random in time can inform the intervention strategies that would be best suited to reduce the risk of further pandemic events.

To determine whether the emergence of new pandemic strains is a memoryless or history-dependent process, we analyse the time periods between influenza pandemics since 1700 statistically under different modelling assumptions. Using Bayesian model selection between exponential and gamma distributions for these time periods, we demonstrate from these small but informative datasets support for the hypothesis of history dependence under eight out of nine sets of modelling assumptions. Using the fitted parameters to make predictions shows a high level of variability in the modelled number of pandemics from 2010–2110.

Though the approach we take relies on limited data, so is uncertain, it provides cheap, safe and direct evidence relating to pandemic emergence, a field where indirect measurements are often made at great risk and cost. Our findings supporting the presence of history dependence enhances the motivation for implementation of active surveillance at the human-animal interface, in particular to elucidate the biological processes behind the observed spacing between pandemics.

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Investigating the dynamics of coupled epidemiological transmission models with application to Group A Streptococcus and Scabies

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Infections with Group A Streptococcus (GAS) are highly prevalent in remote communities in the Northern Territory, Australia. One of the primary drivers of GAS infection is scabies, a small mite which causes a break in the skin layer, potentially allowing GAS to take hold. This biological connection is reaffirmed by the observation that mass treatment for scabies in these remote communities sees a reduction in the prevalence of GAS infection, despite GAS not being directly targeted. In the most extreme case, it has been hypothesised that the eradication of scabies in remote communities may lead to an eradication of GAS related infection.

We start by proposing a model of GAS transmission that assumes that scabies dynamics are at equilibrium. We assume that GAS follows a Susceptible – Infectious – Susceptible (SIS) structure, but individuals who are infected with scabies experience an increased force of infection compared to those who are not infected with scabies. In consequence, we are able to calculate the required prevalence of scabies required to ensure that GAS is eradicated, as a function of R_0 and the coupling strength between the two infections.

In order to more accurately model the impact of mass treatment for scabies, we extend this model to include the dynamics of scabies infections. We consider two different scabies models: one which includes the full dynamics of the scabies mites, and one which collapses these dynamics down to a far simpler phenomenological model. We investigate the difference in the scabies rebound dynamics after mass treatment for these two models, and consider the impact of this difference on the dynamics of GAS. We show that despite the two scabies models having different mean field dynamics, parameter uncertainty and the small population size mean that this difference is severely muted when considering the post-scabies treatment on GAS. Finally, we compute a value for the increased force of infection experienced by those infected with scabies, below which eradication for GAS would be achieved if scabies were eradicated.

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Investigating the effects of childhood vaccination: Rotavirus in Chile

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Rotavirus is a viral disease - mainly transmitted by the fecal-oral mode - that is the leading cause of severe acute gastroenteritis among infants and children less than 5 years of age. The symptoms vary from mild to severe diarrhea with fever and vomiting that may produce rapid dehydration. In most of the cases, severe symptoms require hospitalization and eventually can lead to death.

There exist two licensed rotavirus vaccines that have proven to be safe and effective to prevent rotavirus infections in young children and infants. However, Chile's national childhood immunization program does not currently include vaccination against rotavirus. The disease is responsible for 47% of the hospitalizations of children less than 3 years of age in Chile, which represents an important social and economic burden for the country. We present an ongoing study that is one of the first steps into making public health recommendations for rotavirus control and prevention in Chile, using mathematical models. We developed an ordinary differential equations model that describes the disease dynamics of rotavirus and analyzes the effect of vaccination into the country's hospitalization incidence.

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A structured population model with diffusion in structure space

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A structured population model is described and analyzed, in which individual dynamics is stochastic. The model consists of a PDE of advection-diffusion type in the structure variable. The population may represent, for example, the density of infected individuals structured by pathogen density x , $x \geq 0$. The individuals with density $x = 0$ are not infected, but rather susceptible or recovered. Their dynamics is described by an ODE with a source term that is the exact flux from the diffusion and advection as $x \rightarrow 0^+$. Infection/reinfection is then modelled moving a fraction of these individuals into the infected class by distributing them in the structure variable through a probability density function. Existence of a global-in-time solution is proven, as well as a classical bifurcation result about equilibrium solutions: a net reproduction number R_0 is defined that separates the case of only the trivial equilibrium existing when $R_0 < 1$ from the existence of another - nontrivial - equilibrium when $R_0 > 1$. Numerical simulation results are provided to show the stabilization towards the positive equilibrium when $R_0 > 1$ and towards the trivial one when $R_0 < 1$, result that is not proven analytically. Simulations are also provided to show the Allee effect that helps boost population sizes at low densities.

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Disease modelling: how to control and prevent epidemic outbreaks

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In recent years vaccination studies have led to greater understanding and improvements on the development and distribution of vaccines, especially with respect to certain childhood diseases. However, while current vaccination campaigns strive to achieve herd immunity (a critical threshold of 'immune' individuals needed to protect an entire population from infection), eradication has not been achieved and populations continue to be affected by childhood diseases globally. These outbreaks are usually attributed to the movement of one or more asymptomatic cases from a country affected by

the pathogen in question. Nevertheless, individuals coming from regions with infection-induced immunization can provide protection to the receiving region. Mathematical models are able to describe the dynamics of an infectious diseases in populations, and they can provide important measurements for public health such as the basic reproductive ratio, the vaccination threshold needed to achieve herd immunity, and project the number of cases that could be observed during an outbreak. In particular, metapopulation models can be used to track the movement of individuals through travel or immigration to better understand the movement and persistence of infectious diseases, and border restriction policies. We propose infectious disease models to study the distribution of immunity in a population and how this changes with immigration and travel, by using a Susceptible-Exposed-Infectious-Recovered framework. Our work is in collaboration with Public Health Ontario and has been used to better understand the effects of measles immunity in a population. Our results show that the biggest loss in the susceptible population happens when the infected individual introduced in the population belongs to the group of children between 5 and 9 years, even when vaccination thresholds recommended by the WHO are achieved.

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Infection-acquired versus vaccine-acquired immunity in an SIRWS model

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Waning immunity is known to occur for some infectious diseases after natural infection and vaccination. We present a susceptible-infectious-recovered-susceptible (SIRS)-type transmission model that includes the waning and boosting of immunity. We study how the infection prevalence changes with differences in (i) the durations of infection- and vaccine-acquired immunity and (ii) the assumed mechanism through which immune boosting acts to extend protection.

Our results show that increasing vaccine uptake always lowers the proportion of primary infections but may lead to an increase in overall transmission. Where the boosting of vaccine-acquired immunity delays a primary infection, the driver of transmission largely remains primary infections. In contrast, if immune boosting bypasses a primary infection, secondary infections become the main driver of transmission under sufficiently long-lasting vaccine-induced immunity. Our study highlights that for a particular disease and associated vaccine, a detailed understanding of how the duration of protection can influence infection prevalence is important as we seek to optimise vaccination strategies.

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Role of household size and community structure on the spread of tuberculosis

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Some northern communities in Canada see inordinately high tuberculosis incidence compared to the rest of the country. Most of the affected locations are isolated First Nations communities and while

this means that the usual argument of tuberculosis as an indicator disease of poverty is applicable, it does not explain the specifics of the situation. To try to understand the role of the various factors at play, we focus on two specific aspects: household size and community structure. We investigate this using a simple discrete-time model for households, which we study analytically and with numerical simulations.

This is joint work with Ryan Sherbo.

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Dynamical models of tuberculosis transmission and optimal treatment strategies in the Republic of Korea and Philippines

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In this talk, we will present several mathematical models of tuberculosis (TB) based on the reported data in the Republic of Korea and Philippines, and also propose the optimal treatment strategies depending on the various scenarios in each country. Korea has ranked the highest TB incidence among members of the Organization for Economic Cooperation and Development (OECD). TB is the sixth leading cause of morbidity and mortality in the Philippines. The least-square curve fitting have been used for best fitting the parameters in our models to the observed data. To determine the optimal intervention strategy which is reducing the number of exposed and infectious individuals and the cost of control measures, optimal control theory was used [1]. Important issues has been addressed from our research: implementing the smoking controls, not with TB controls, can derive significant reduction of the incidence of TB transmission [3]. We suggested the rearrangement of the Korean government TB budget based on optimal treatment strategies from modelling [2]. Finally, in the Philippines enhancing active finding control is a significant control factor to curtail the spread of TB [4].

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Feasibility and stability properties of complex ecological networks: New perspectives / 284

Most ecological communities are at the limit of structural stability: the evidence

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An ecological community is called *structurally unstable* if it is feasible (a positive equilibrium exists) but feasibility is sensitive to changes in parameters, external pressures, or species composition. Absent such sensitivities, a feasible community is called *structurally stable*.

Mathematically one can show that, due to amplification of perturbations through indirect interactions, structural stability of ecological networks declines with increasing species richness (a negative complexity-stability relation). At some limiting richness structural instability sets in, thus imposing an inherent limit to sustainable biodiversity. Under sustained invasion pressure this limit is naturally reached, stabilizing species richness despite ongoing temporal turnover in composition.

We argue that the combined mathematical, numerical and empirical evidence strongly suggests that most natural ecological communities are indeed close to this limit. This applies to both local and regional scales. At local level, structural instability mechanistically explains, e.g., observed biodiversity patterns across trophic levels and body size; the observed magnitude of indirect interactions; the known high parameter sensitivity of food-web models; and the absence of clear complexity-stability relations in realised communities. At regional level, structural instability mechanistically explains, e.g., observed species area relations and range-size distributions. We urge ecologists to devote more research to the study of ecological network models at the limit of structural instability, because these tend to have particular properties that are commonly found in nature, but not in their structurally stable counterparts.

Feasibility and stability properties of complex ecological networks: New perspectives / 307

Statistical properties of the equilibria of large random ecosystems

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The consensus that complexity begets stability in ecosystems was challenged in the seventies, a result recently extended to ecologically-inspired networks. The approaches assume the existence of a feasible equilibrium, i.e. with positive abundances. However, this key assumption has not been tested. We provide analytical results complemented by simulations which show that equilibrium feasibility vanishes in species rich systems. This result leaves us in the uncomfortable situation in which the existence of a feasible equilibrium assumed in local stability criteria is far from granted. We extend our analyses by changing interaction structure and intensity, and find that feasibility and stability is warranted irrespective of species richness with weak interactions. Interestingly, we find that the dynamical behaviour of ecologically inspired architectures is very different and richer than that of unstructured systems. Our results suggest that a general understanding of ecosystem dynamics requires focusing on the interplay between interaction strength and network architecture.

Feasibility and stability properties of complex ecological networks: New perspectives / 451

How does diversity relate to feasibility and stability properties of complex ecological networks?

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A central debate when studying ecological communities concerns the relative importance of selective processes relative to stochastic ones. This has significance for understanding the dynamic behaviour of these systems, for assessing features such as fragility and resilience, and ultimately, for determining how to correctly approach them. At the core of dealing with this challenge is the need to link

‘observed patterns’ with the ‘underlying processes’ that created them; this is a long-standing well known challenge in the arenas of ecology and evolution. The application of networks in ecological theory can provide a useful perspective and toolkit for dealing with this challenge. Indeed, in many cases the selective forces acting on individual species are frequency dependent and hence need to be placed in a community framework in order to understand their ecological role as it depends on the rest of the network, and how the functioning of the whole network depends on them.

Diversity has played a central role in most studies that address the relationships between structure and function in ecological-network. Here I discuss different views on the concept of diversity, both as an indicator of system functioning and as an emergent property of these systems. As a case study I specifically focus on pathogen communities, where ecological and evolutionary feedbacks act on short time scales.

Feasibility and stability properties of complex ecological networks: New perspectives / 312

When Google meets Lotka-Volterra

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In his theoretical work of the 70's, Robert May introduced a Random Matrix Theory (RMT) approach for studying the stability of large complex biological systems. Unlike the established paradigm, May demonstrated that complexity leads to instability in generic models of biological networks having random interaction matrices A . Similar random matrix models have since been applied in many disciplines. Central to assessing stability is the “circular law” since it describes the eigenvalue distribution for an important class of random matrices, A . However, despite widespread adoption, the “circular law” does not apply for ecological systems in which density-dependence operates (i.e., where a species growth is determined by its density). Instead one needs to study the far more complicated eigenvalue distribution of the community matrix $S = DA$, where D is a diagonal matrix of population equilibrium values. Here we obtain this eigenvalue distribution. We show that if the random matrix, A , is locally stable, the community matrix, $S = DA$, will also be locally stable, providing the system is feasible (i.e., all species have positive equilibria $D > 0$). This helps explain why, unusually, nearly all feasible systems studied here are locally stable. Large complex systems may thus be even more fragile than May predicted, given the difficulty of assembling a feasible system. The degree of stability, or resilience, was found to depend on the minimum equilibrium population, rather than factors such as network topology. For studying competitive and mutualistic systems, our analysis is only achievable upon introducing a simplifying “Google-matrix” reduction scheme. In this talk we will explain what happens “when Google meets Lotka-Volterra.”

Feasibility and stability properties of complex ecological networks: New perspectives / 458

A mechanism for metacommunity-scale biodiversity regulation

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There exists a growing body of empirical evidence that suggests biodiversity regulation – the emergence of dynamic equilibrium diversity – may be a common or even general feature of ecosystems. However a mechanistic understanding of what tends to constrain diversity in nature remains elusive. Here we introduce a metacommunity assembly model in which regional diversity converges

on dynamic equilibria, despite continuous species turnover (temporal β -diversity). We build on previous theoretical studies of local biodiversity regulation by arguing that the mechanism controlling these temporal diversity patterns is the loss of Ecological Structural Stability – a diversity dependent measure of the sensitivity of an ecological assemblage to perturbation. As the limit of structural stability is approached, macroecological patterns characteristic of natural assemblages emerge in model metacommunities. In particular, the species abundance distribution, range size distribution, species co-occurrence profile, and species area relation all match patterns observed robustly in the field. These results suggest that structural instability is an important macroecological organising principle.

Fluids & blood / 238

A model of vascular refilling with inflammation

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Monitoring the fluid status of end-stage renal disease (ESRD) patients remains an important aspect in hemodialysis. Recently, de los Reyes *et al.* developed a two-compartment model describing vascular refilling with ultrafiltration during short-term hemodialysis in ESRD patients. Ultrafiltration is taking out fluid from the vascular space; and vascular refilling occurs through the capillaries and by lymph flow, driven by pressure and concentration gradients in the plasma and interstitial spaces. A feature common in ESRD patients on hemodialysis is inflammation. Inflammation is believed to greatly contribute to the progression of cardiovascular disease, the most common cause of mortality among hemodialysis patients. Increased vascular permeability associated with inflammation is likely to influence the capillary wall properties that may cause perturbations affecting capillary refilling. We propose a way to quantify inflammation by considering the concentration of the inflammatory biomarker C-reactive protein (CRP). A model that incorporates inflammation to the vascular refilling model is presented. Simulations and parameter estimation related to CRP and capillary wall properties are also presented.

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Exploring differential regulation of blood clot degradation

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Blood clots are physiologically degraded via a biochemical cascade initiated by tissue plasminogen activator (tPA). tPA, which is also used clinically to treat stroke, creates plasmin, the main protein involved in degradation. We explore the effects of tPA unbinding and diffusion on clot degradation. We propose that plasmin can “force” tPA to unbind from the clot, which has significant implications for the resulting clot degradation. Using a 3-dimensional stochastic multiscale model, four different

regulatory mechanisms are explored when tPA is forced to unbind: 1) tPA is immediately able to rebind to fibrin; 2) tPA is immediately removed from the system; 3) tPA is bound to a fibrin degradation product (FDP) that is small enough to diffuse through the clot, and after some time determined by the kinetic unbinding rate, the tPA unbinds from the FDP and is available for rebinding; 4) tPA is bound to an FDP that can only diffuse along or away from the clot (due to its size), and after some time determined by the kinetic unbinding rate, the tPA unbinds from the FDP and is available for rebinding. We discuss the contributions of each mechanism in clot degradation, the surprising role of plasmin, and the implications for stroke treatment.

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Modelling the Endothelial Glycocalyx layer in the microcirculation using homogenisation

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The Endothelial Glycocalyx Layer (EGL) is a porous macromolecular layer that lines the insides of blood vessels. It is located on the important interface between the endothelium and flowing blood and as such is believed to play a number of important roles including transducing mechanical signals from flowing blood and regulating vessel permeability. Previous work modelling the EGL at the continuum level has typically assumed that it is a homogenous isotropic porous media and that if deformable; it does so as a linear-elastic block. In this work, we use homogenisation theory to derive a more sophisticated model of the EGL that takes into account what is known about the underlying periodic microstructure of the EGL.

Homogenisation theory is a method of multiple scales that allows us to exploit the periodicity in the problem as well as the much smaller length scale (compared to the macroscopic scale) over which this periodicity exists. This allows us to derive an overall continuum level model of the EGL that takes into account this microstructure while still retaining a lower level model for the flow around the microstructure. In deriving this model, we find that it differs from other fluid flow models typically obtained from homogenisation theory as the EGL is only periodic tangentially to the vessel surface and not normally.

This more sophisticated model allows us to investigate the effects of anisotropy in the model at the continuum level as endowed by the geometry of its microstructure. In addition, the underlying microstructural model allows us to obtain measures such as the solid shear stress experienced by the endothelium and the torque induced by flow over the EGL that cannot be directly obtained from previous continuum level models and is an important measure for functions such as mechanotransduction.

From solitary swimmers to coordinated groups: Modelling motion in fluids at very low Reynolds number / 298

Flagellar swimming in viscoelastic fluids

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Many important biological functions depend on microorganisms' ability to move in viscoelastic fluids such as mucus and wet soil. The effects of fluid elasticity on motility remain poorly understood partly because the swimmer strokes depend on the properties of the fluid medium, which obfuscates the mechanisms responsible for observed behavioural changes. We use experimental data on the gaits of *Chlamydomonas reinhardtii* swimming in Newtonian and viscoelastic fluids as inputs to numerical simulations that decouple the swimmer gait and fluid type in order to isolate the effect of fluid elasticity on swimming. In viscoelastic fluids, cells employing the Newtonian gait swim faster but generate larger stresses and use more power, and as a result the viscoelastic gait is more efficient. Furthermore, we show that fundamental principles of swimming based on viscous fluid theory miss important flow dynamics: fluid elasticity provides an elastic memory effect which increases both the forward and backward speeds, and (unlike purely viscous fluids) larger fluid stress accumulates around flagella moving tangent to the swimming direction, compared to the normal direction.

From solitary swimmers to coordinated groups: Modelling motion in fluids at very low Reynolds number / 197

Chemotaxis Modelling for Sperm Motility

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An important aspect in the study of reproduction is how sperm are guided toward an egg for fertilization. One such mechanism is the process of chemotaxis, in which the sperm detect changes in concentration (namely of Ca²⁺) in the fluid environment and utilize these changes to alter the waveform of their flagellar beat. This change in beat form results in changes to the swimming path. We model the swimming sperm using a Kirchhoff elastic rod model coupled with the method of regularized Stokeslets for the fluid motion. In order to simulate the effect of chemical concentrations, we employ a stochastic decision making process.

From solitary swimmers to coordinated groups: Modelling motion in fluids at very low Reynolds number / 108

Understanding pattern formation in interacting cell populations

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Tissue development requires cells of different types to organise themselves into the appropriate patterns and structures to produce viable, functional tissue. Similar processes occur in tissue repair (e.g. wound healing) or when tissues are grown in vitro (tissue engineering). Understanding how this organisation is coordinated is therefore an important basic problem in biology and medicine.

I will present results from agent-based modelling of interacting cell populations, and illustrate how different interactions between the cells affect the patterns of cell organisation observed in tissues. I

will explain how these patterns can be quantified using pair-correlation functions, and discuss the extent to which we can infer cell interactions from observed tissue-scale patterns.

From solitary swimmers to coordinated groups: Modelling motion in fluids at very low Reynolds number / 101

Fast algorithms for the dense matrices arising from the Method of Regularized Stokeslets

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The swimming motion of microorganisms such as sperm and cilia can be modelled by several methods, all of which entail solving equations of fluid-structure interaction. Among them, the Method of Regularized Stokeslets (MRS) and the Rotne-Prager-Yamakawa tensor have the advantage of not requiring a 3D Eulerian grid and using the fundamental solutions to the underlying equations instead. However, the computations required by both methods entail the use of dense matrices, and they tend to be large and very costly to work with for practical models in which the number of micro-swimmers is large.

The ‘data-sparse’ structure of these matrices enables the development of fast algorithms. To compute the matrix-vector products efficiently, we extend the Kernel-Independent Fast Multipole Method (KIFMM) to the kernels associated with the MRS. To solve linear systems with the same matrices efficiently, we consider both a data-sparsifier preconditioner and a block-diagonal preconditioner; to expedite the application of the preconditioners, we employ a number of techniques such as Krylov subspace recycling. We apply the proposed algorithms to study the dynamics of a large group of sperm and the flow field induced by a carpet of cilia.

From solitary swimmers to coordinated groups: Modelling motion in fluids at very low Reynolds number / 275

Exploring the fluid dynamics of collective pulsing behaviour in xeniid corals using the immersed boundary method

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Xeniid corals, a family of soft corals (*Alcyonacea*), include species displaying a unique pulsing behaviour. Within a colony, each individual polyp pulses by actively contracting and passively expanding eight tentacles, increasing the local mixing and enhancing nutrient and gas exchange. Using the immersed boundary method with finite elements (IBFE), we constructed a 3D model of a pulsing polyp. The motion of the polyp tentacles is based on actual motion data tracked from videos of real polyps. We find that individual polyps pull water in radially, mix it between their tentacles, and expel the fluid volume in an upward jet. After validating this 3D IBFE model against experimentally measured flow fields, we are now using the model to numerically simulate small groups of polyps and to quantify the effects of collective pulsing behaviour on the local fluid dynamics. Here, we simulate pairs of polyps and vary the pulsing patterns (in-phase and different degrees of out-of-phase)

and distance between polyps to better understand how differences in collective pulsing behaviour affect local flow and mixing.

Frontiers in viral dynamics / 69

Characterizing SHIV infection *in vitro* and *in vivo*

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The host range of human immunodeficiency virus (HIV) is quite narrow. Therefore, analyzing HIV-1 pathogenesis *in vivo* has been limited owing to lack of appropriate animal model systems. To overcome this, chimeric simian and human immunodeficiency viruses (SHIVs) that encode HIV-1 Env and are infectious to macaques have been developed and used to investigate the pathogenicity of HIV-1 *in vivo*. So far, we have many SHIV strains that show different pathogenesis in macaque experiments. However, dynamic aspects of SHIV infection have not been well understood. To fully understand the dynamic properties of SHIVs, we focused on two representative strains – the highly pathogenic SHIV, SHIV-KS661, and the less pathogenic SHIV, SHIV-#64 – and measured the time-course of experimental data in cell culture and rhesus macaque and analyzed them. I would like to discuss our quantitative results and future direction of this study.

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Optimising and understanding new HIV therapies

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One of the main focuses of HIV research today concerns allowing people living with HIV to experience prolonged periods where they do not need to remain on treatment. Current therapies are able to suppress HIV to undetectable levels, however as soon as therapy is interrupted the virus “re-bounds” to pre-treatment levels and this leads to increased morbidity from HIV. This rebound likely occurs as a result of long-lived latently infected cells, which persist in spite of therapy as part of a ‘latent reservoir’. Recent work has focused on reducing the size of the latent reservoir in the hope this will increase the time subjects can remain off therapy.

We set up a model of HIV remission and viral reactivation and used this to estimate both the probability of viral rebound even with a reduced latent reservoir, and also the optimal reduction in reservoir size that both minimises drug exposure, and maximises treatment effect.

Using a stochastic model we show that a treatment that achieves an average of a one-year viral remission will still lead to nearly a quarter of subjects experiencing viral rebound within the first three months and give rise to an expected 39 (95%UI 22-69) heterosexual transmissions and up to 262 (95%UI 107-534) homosexual transmissions per 1,000 treated subjects over a 10-year period.

Additionally, using a deterministic model we investigated the trade-off between increasing the average duration of remission, versus the risk of treatment failure (viral recrudescence) and the need for re-treatment. To minimise drug exposure, we find that the optimal treatment would increase the average time of viral rebound to 30 years. Interestingly, this is a significantly lower level of reduction than that required for complete elimination of the viral reservoir, but significantly longer

than is currently being targeted. We show that when shorter periods are targeted, there is a real probability of viral transmission occurring in between the times at which subjects would be tested for viral rebound.

Our work shows that while therapies designed to reduce the size of the latent reservoir present a promising avenue of research, prior to widespread implementation of such strategies, the possibilities and consequences of viral reactivation from latency must be adequately considered.

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Investigating the mechanisms of influenza viral interference using within-host models based on a ferret re-exposure experiment

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Viral interference, whereby infection with one type of virus may temporarily “protect” the host from subsequent infection with another virus has been described for a number of influenza strains and in a number of different host species. In particular, experiments performed in ferrets with influenza A(H1N1)pdm09, A(H3N2) and B have demonstrated strong levels of interference dependent upon the particular virus pair, order of infection and precise timing of re-exposure. Mathematical modelling, which aims to capture the viral time course of the re-exposure behaviour based on plausible immunological mechanisms, is a particularly useful tool to study viral interference, opening up a new approach to advancing our understanding of viral dynamics and the host immune response.

In this talk, I will first briefly describe the ferret re-exposure experiments performed by our collaborators. In the experiments, naïve ferrets were inoculated with one virus (i.e. primary infection) and subsequently exposed to another (to induce the secondary infection) after a certain time interval (1 – 14 days). Viral interference was observed when the inter-exposure interval was less than a week. Furthermore, viruses differed in their ability to induce a protective immune response against subsequent exposure.

I will then introduce the model-based approaches that we have used to investigate immune-mediated viral interference. We begin with a qualitative approach by introducing and analysing a family of within-host models of re-exposure viral kinetics which differ in their hypothesised mechanisms of action for the non-specific innate immune response. We assumed that different viruses stimulate the innate immune response to different degrees and demonstrate the models’ ability to qualitatively reproduce the observed viral shedding profile in the secondary infection for short inter-exposure intervals (less than 5 days). We then extend the models by incorporating cross-reactive adaptive immunity (in particular CD8+ T cells), which provides an explanation of the viral shedding profile of the secondary infection for longer inter-exposure intervals (5-14 days).

Finally, I will briefly describe our most recent efforts to calibrate the proposed models to the re-exposure data in a Bayesian framework, providing quantitative insight. Through this approach, we have shown that models fitted to the re-exposure data are able to predict the outcome of viral interference more accurately than models fitted only to the data from a single infection.

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Predicting mechanism of action and quantifying anti-viral effects of cytokines against hepatitis B virus

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Hepatitis B Virus (HBV) is widespread infectious disease and more than 240 million people are chronic infected so far. Although some patients can suppress the viral load under detection limits by current drug treatments, these are not effective for over 60% of patients. The obstacles for developing effective drugs are the existence of a reservoir in infected cells, which is known as covalently closed circular DNA (cccDNA). Because cccDNA remains in infected cells for a long time, the replication of HBV is not completely inhibited. We need new effective drug that can decrease the concentration of cccDNA persistently. In this study, we carried out cell culture experiments that can be measured the time course of the concentration of cccDNA, intracellular HBV DNA and extracellular DNA. Then, we added several kinds of cytokines in this experiment, and measured the same time course data. Furthermore, to investigate mechanism of action and quantify the anti-viral effect of each cytokine, we established a mathematical model that can capture the dynamics of intracellular HBV replication and fitted this model to the our time course data. Finally, we investigated which cytokines can decrease the concentration of cccDNA. This framework that combining viral experiment and mathematical model would be helpful to find a chemical that have desired mechanism of action.

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Spatial moment description of birth-death-movement processes incorporating the effects of crowding and obstacles

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Birth-death-movement processes, modulated by interactions between individuals, are fundamental to many biological processes such as development, repair and disease. Similar interactions are also relevant in ecology. A key feature of the movement of cells within *in vivo* environments are the interactions between motile cells and stationary obstacles, such as the extracellular matrix and stationary macromolecules. Here we propose a multi-species individual-based model (IBM) of individual-level motility, proliferation and death. In particular, we focus on examining the case where we consider a population of motile, proliferative agents within an environment that is populated by stationary, non-proliferative obstacles. To provide a mathematical foundation for the analysis of the IBM, we derive a system of spatial moment equations that approximately governs the evolution of the density of agents and the density of pairs of agents. By using a spatial moment approach we avoid making the usual mean field assumption so that our IBM and continuous model are able to predict the formation of spatial structure, such as clustering and aggregation. We explore several properties of the obstacle field, such as systematically varying the obstacle density, obstacle size, and the nature and strength of the interactions between the motile, proliferative agents and the stationary, non-proliferative obstacles. Overall we find that the spatial moment model provides a reasonably

accurate prediction of the dynamics of the system, including subtle but important effects, such as how varying the properties of the obstacles leads to different patterns of clustering and segregation in the population.

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An agent-based model for pseudohyphal yeast growth

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Budding yeasts, such as *Saccharomyces cerevisiae* (baker's yeast), that are grown on a solid substrate are able to alter their growth pattern to suit the surrounding nutrient level. When nutrient is readily available, buds separate from the mother cell to produce colonies that appear close to circular when viewed from above. When nutrient is limited, the cells reproduce via the pseudohyphal growth pattern, which is characterised by distal unipolar budding (budding opposite to the birth scar), the elongation of cells and a persistent connection between mother and daughter cell. This change results in the growth of filaments directed away from the colony, producing an irregular shape. The precise shape of the colony is dependent on several factors, such as the nutrient level and strain, while gene-deletion mutants may also display different morphologies. As these have an influence at the cell level, there is a need to understand how the behaviour of individual cells influences the overall colony morphology. To address this, yeast colony growth is studied using an agent-based mathematical model. The model allows for the control of nutrient diffusion and budding mechanism, including the change in cell behaviour during the pseudohyphal phase. Simulations using this model are found to compare favourably with experimental observations and are used to illustrate the relationship between the behaviour of individual cells and the overall colony shape.

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A hyperbolic curvature flow for biological tissue growth and its application to determine cell behaviour during the infilling of irregular pores

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The growth of several biological tissues is known to be controlled by local geometrical cues, such as the curvature of the tissue interface. Geometry modulates cells collectively through the evolving space available to the population of cells, but it may also modulate the individual behaviours of cells. In this contribution, I will first present how the influence of curvature on the collective crowding or spreading of cells growing new tissue leads to a new type of hyperbolic curvature flow (with curvature-dependent normal acceleration) for the evolution of the tissue interface. Depending on the strength of diffusive damping, the model exhibits complex growth patterns such as undulating motion, efficient smoothing of irregularities, and the generation of cusps. Insights into these growth patterns are provided by analysing the shock structure in the zero-diffusion and infinite-diffusion limits. In a second part, I will present how this model can be used with experimental data on the infilling of irregular bone pores to single out the collective influence of geometry, and gain access to the geometric regulation of individual cell behaviours.

HIV / 11

Staged HIV transmission and treatment in a dynamic model with concurrency

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HIV progression studies have asserted three stages: acute infection, chronic infection, and AIDS. We develop a model with three stages and include an infection class with non-uniform Highly Active Anti-Retroviral Treatment leading to viral suppression. Capturing the incidence rate of HIV in minority U.S. women requires a model stratified by race/ethnicity and sexual behaviour in addition to assumptions of assortative partner choice and concurrent relationships. We include the effect of concurrency following the work of Watts and May (1992, Math. Biosciences) who in a simple deterministic model allowed for overlapping partnerships and infection from either a new sexual partner or a longtime partner who was uninfected at the start of the partnership. This model was hampered by the assumption of a latent phase which generated a non-autonomous system. We present a new autonomous deterministic model of the effect of concurrent sexual partnerships that allows for an analytical study of disease transmission. We incorporate the effect of concurrency through the newly derived force of infection term in a mathematical model of the transmission of HIV through sexual contact in a population stratified by sexual behaviour and race/ethnicity. Time series analysis, as well as parameter sensitivity analysis, determine which strategy has the largest impact in the short and long term. Interventions focused on encouraging chronically infected into viral suppression, as well as interventions focused on maintaining viral suppression have the largest impact on the long term dynamics, and the latter having the largest impact on the heterosexual community due to current racial disparity in treatment. While reducing concurrency likelihood and duration positively impacts the long term dynamics, left unchecked, an increase in concurrency will significantly raise the values of the endemic equilibrium.

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Studying the effect of pre-exposure prophylaxis on the dynamics of different populations susceptible to HIV

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Pre-exposure prophylaxis is a useful method for the preventing the transmission of HIV to susceptible individuals. What target population would provide the biggest impact on HIV dynamics? To answer this question, we present a differential equation model stratified by behavioural risk and sexual activity. Some susceptible individuals have higher rates of risky behaviour that increase their chance of contracting the disease. Similarly, infected individuals with risky behaviours are at higher risk of transmitting the disease to a susceptible individual. We further divide the infected population by their diagnosis status. We define model parameters for both the urban case, or high-density sexual network, and the national case, or mixture of low- and high-density sexual network. Our results indicate that the undiagnosed high-risk infected group is the largest contributor to the epidemic. Our model suggests that when pre-exposure prophylaxis is applied to the susceptible populations, its effectiveness extends outside of the group that is taking the drug, providing herd immunity. Our models suggest that a strategy targeting the high-risk susceptible population would have the largest impact. We also find that such a protocol has similar effects for the national and the

urban case, despite the smaller sexual network found in rural areas. To further analyze the effect of herd immunity and network density, we simulate our model using a random walk. The parameters are summarized and reduced to include sexual contact rate, behaviour riskiness, medication adherence, and diagnosis rate. These parameters are described using probability distributions, and the status of an individual at each iteration is determined by random draws from those distributions and a control equation. Susceptible individuals' adherence to pre-exposure prophylaxis modifies their transmission risk term. We simulate under both urban and national network conditions, as well as low-density or rural sexual network conditions. The effect of different adherence distributions is also analyzed over varying proportions of susceptible individuals on pre-exposure prophylaxis medications. We hope this method will better illuminate the herd immunity effect provided by targeting high-risk susceptible individuals on different sexual networks.

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Contribution of mass incarceration to HIV and optimal control of SIR model

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We develop a Susceptibles, Infected and Recovered (SIR) type mathematical model of HIV epidemiology to explore a possible mechanism by which mass incarceration can lead to increased HIV incidence. The results are particularly relevant for the African American community in the United States that represents only 12% of the total population but accounts for 45% of HIV diagnoses and 40% of the incarcerated population. While most explanations of the link between mass incarceration or anything else that leads to a population with a low ratio of males to females and higher HIV burden are based on the complicated idea of sexual concurrency, we propose a much simpler mechanism based on the idea of sexual activity compensation. The pool of men will increase their sexual activity to meet the demands of the female population. Through mathematical analysis and numerical simulation, we demonstrate that these assumptions produce a situation in which mass incarceration lead to higher HIV incidence.

We also develop an optimal control model of SIR type. In this model, the control is education or information given to the public to manage a disease outbreak when effective treatments or vaccines are not readily available or too costly to be widely used. We study stability analysis and use optimal control theory on the system of differential equations to achieve the goal of minimizing the infected population. We illustrate our results with some numerical simulations.

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Majority decisions by four or five members: rules that can be formed and maintained in viral populations to exclude free riders.

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Most of the viral gene products are shared among a viral population in a host cell, which accumulates up to 10^6 to 10^7 genomes. High mutation rates in viral genome replication bring genetic variety to the intracellular population, and this makes the situation social: mutant genomes that do not code intact gene products can survive as free riders, by using the gene products from the other genomes in the intracellular population. We have previously shown that two plant RNA viruses, Japanese soil-borne wheat mosaic virus and tomato mosaic virus, infect a host cell by 5-6 and ~4 genomes in average, respectively, and proposed that this cell infection by a limited number of genomes enhance stochastic separation of free riders from others, resulting in exclusion of free riders from the whole population [1,2]. Here we simulated the evolution of average number of viral genomes to infect a cell (multiplicity of infection, or MOI, in virology). The simulation showed that MOI evolves to 4-5 *in silico*. This result could be explained by a balance between exclusion of free riders by smaller MOI and avoidance of stochastic failure of infection. Consistently, our further experiments showed that a tripartite plant RNA virus, cucumber mosaic virus (CMV), also has MOIs of 3-5 for its multiple genomic segments in multiple hosts.

The MOI of 4-5 does enhance separation of free riders from others, but still allows their co-existence for a certain period of time. This requires “decisions” by viruses. The intracellular populations exclusively consisting of free riders cannot infect new adjacent cells, and those exclusively consisting of intact genomes will infect the adjacent cells at high probability; those consisting of both free riders and intact genomes need to decide whether to infect the adjacent cells, depending on the ratio of free riders in each intracellular population. Our simulations showed that a majority-decision-like system, where the cell-to-cell infection probability sharply changes between 0 and 1 at a certain threshold for the ratio of free riders, can be favoured by plant viruses. The simulation result was supported by a co-inoculation experiment of CMV variants that carry a functional cell-to-cell movement protein gene or a dysfunctional one.

[1] Miyashita and Kishino (2010) “Estimation of the size of genetic bottlenecks in cell-to-cell movement of soil-borne wheat mosaic virus and the possible role of the bottlenecks in speeding up selection of variations in trans-acting genes or elements.” *J Virol* 84(4) 1828-1837.

[2] Miyashita, Ishibashi, Kishino and Ishikawa (2015) “Viruses roll the dice: the stochastic behavior of viral genome molecules accelerates viral adaptation at the cell and tissue levels.” *PLOS Biol* 13(3) e1002094.

Host-parasite coevolution in space / 130

Cell-free versus cell-to-cell viral transmission in a spatial structure

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Viruses have two modes spread in a host body, one is to release infectious particles from infected cells (cell-free) and the other is to infect directly from an infected cell to an adjacent cell (cell-to-cell). Since the mode of spread affects the evolution of life history traits, such as virulence, it is important to reveal which mode is selected. Here we show the evolutionarily stable proportion of cell-free and cell-to-cell infection, and how it depends on the spatial distribution of target cells. Using an epidemic model on a 2D regular lattice, we consider the infection dynamics by pair approximation and check the evolutionarily stable strategy. We also conduct the Monte-Carlo simulation to observe evolutionary dynamics. We show that a higher cell-to-cell infection is selected as target cells become

clustered. The selected strategy depends not only on the degree of clustering but also the abundance of target cells per se.

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Host-parasite co-evolution in space: it's reproduction that really matters

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The impact of spatial structure on evolutionary outcomes can be profound due to both ecological and genetic correlations. One of the best developed areas of spatial evolutionary theory has focused on the coevolution of hosts and parasites. There are profound impacts of local as opposed to global infection on both parasite and host evolutionary outcomes. Using a combination of pair approximations to apply approximate adaptive dynamics to spatial models and simulations we show the central importance of reproduction to the outcome. For example spatial effects on the evolution of resistance arise to due less costly local reproduction rather than spatial epidemiological patterns, the host spatial structure that is created by local reproduction has profound effects on parasite evolution even if transmission is mostly global and the impact of disease on reproduction rates impacts ESS virulence. This highlights the importance of indirect spatial effects on the spatial evolutionary ecology of focal traits.

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Causes and potential consequences of conditional host dispersal: the importance of spite in host populations

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Spatial structure owing to localized dispersal in hosts can have dramatic impacts upon the coevolutionary dynamics of hosts and parasites. The basic idea is that localized dispersal in hosts can lead to localized transmission, thereby selecting for costly resistance in hosts and lower virulence in parasites. Both of these evolutionary forces are grounded on the altruism (i.e., costly to the actor but beneficial to recipients). From the viewpoints of the hosts, however, they can also utilize the pathogens to harm their neighbors (biological weapon hypothesis), thereby gaining positive inclusive-fitness benefits overall. Despite this, few studies looked at the causes and consequences of host dispersal evolution. Here, using mathematical models of inclusive fitness theory, we show three understudied ideas. First, differential costs of dispersal between susceptible and infected individuals can modify the host population structure. Second, if hosts can condition their dispersal propensity depending on the sickness (susceptible or infected), then the evolutionary dynamics of such conditional host dispersal can generate evolutionary bistabilities such that dispersal propensity biases towards susceptible or infected individuals depending on the initial conditions of the host populations. Finally, we propose that such drastically different dispersal propensity could turn over the classic idea that spatial structure can often favour increased resistance: rather, differential costs of dispersal and/or conditional dispersal propensity in hosts could favour “spite” of the hosts, which has been largely

ignored aspects in spatially structured host-parasite dynamics. We overall highlight the neglected but profound aspects of host dispersal.

How mixing generates spatial gradients significant to signalling, waste removal, and the distribution of microorganisms / 471

Spike trains to force generation

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The field of neuromechanics, which attempts to integrate neural control with muscle activation and the resulting movement of an organism, is an emerging field of organismal biology. Approaches from experimental biology, robotics, and mathematics have now reached the point where their knowledge about the different facets of (animal) locomotion can be combined and integrated into realistic and useful models. This integration between fields opens up new questions and problems for researchers to solve. In this talk, we explored the interface between neuron and muscle during the initial transfer of information that generates muscle contraction.

Muscle contraction occurs when neuron action potentials stimulate the sarcoplasmic reticulum, releasing calcium ions that then bind to muscle filaments, allowing the myosin to contract the muscle. We will present a model that couples spike-train activation to mass-action equations for calcium ions, which in turn couples to the Hill model for muscle contraction force-velocity relationship. This model allows for investigation of spike trains required to produce partial twitch response, and total tetanic contraction.

How mixing generates spatial gradients significant to signalling, waste removal, and the distribution of microorganisms / 126

Oocyte fertilisation, chemical signalling and waves

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It has been known for some decades that fertilisation of some amphibian and fish eggs is followed by a wave of calcium ions over the surface of the egg, which is associated with a physical change to the surface. Similar waves are seen at other stages of embryonic development. An unfertilized mammalian egg is surrounded by cumulus cells to form a cumulus-oocyte complex (COC). Just a few years ago, medical researchers at the University of Adelaide identified, for the first time, a wave-like behaviour of the cumulus cells in COCs after sperm had been added to the culture medium, believed to be a response to fertilisation. From the speed of the wave it was inferred that the cells were responding to one or more chemical signals from locations on the surface of the egg and that calcium ion concentration was the likely signal. More recently it has been determined that the wave is associated with cumulus-cell death.

I will describe some ongoing modelling and experimental work being undertaken to explain the behaviour of the cumulus cells, assuming the wave is initiated at the fertilisation site. We will examine whether a chemical release by either or both of the oocyte and cumulus cells is qualitatively consistent with experimental observations.

How mixing generates spatial gradients significant to signalling, waste removal, and the distribution of microorganisms / 194

Mixing and pumping by pairs of helices in a viscous fluid

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It is difficult to mix and pump fluid in microfluidics devices because the traditional methods of mixing and pumping at large length scales don't work at small length scales. Experimental work has suggested that rotating helical flagella may be used to effectively mix and pump fluid in microfluidics devices. To further explore this idea and to characterize the flow features around rotating helices, we study the hydrodynamic interactions between two rigid helices rotating at a constant velocity. Helices are coupled to a viscous fluid using a numerical method based upon a centerline distribution of regularized Stokeslets, and we analyze the effects of spacing and phase shift on mixing and pumping.

How mixing generates spatial gradients significant to signalling, waste removal, and the distribution of microorganisms / 361

Flow and movement of organisms through protective layers

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Microscale filtering and protective layers appear in a variety of places throughout the biological world, with examples including both internal physiological examples (extracellular proteins, microvilli, cilia) and external biological structures (trichomes, swimming legs, bristled wings). In this talk, I describe an agent-based framework built for exploring the biological environment created by these structures and its potential effect on small, lightweight organisms. Using implemented analytical models (e.g. Brinkman) or input from CFD packages to specify the flow field, the framework can simulate a large variety of behaviours in both 2-D and 3-D time-varying environments as a testing ground for population-level theory. Preliminary numerical results will be shown demonstrating some of the capabilities of the approach as well as future directions.

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Mathematics of wildlife smuggling interdiction

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The illegal trade of wildlife is estimated to run into hundreds of millions of dollars. It is an international problem that exploits both enforcement loopholes and corruption, and it is a direct threat to the survival of plant and animal species. Smugglers transport wildlife and their derivatives from

sources to destinations across the globe. They are able to choose the route they take to move these commodities across international borders. The location where a smuggler enters a country is important as limited biosecurity resources are able to be placed at these locations. The locations and amount of biosecurity resources must be allocated intelligently. Quantitative analysis and mathematical methods are required to provide insights into illegal wildlife trade networks. In this talk, I will discuss a novel two player game on a network between smugglers and biosecurity agencies which looks at how best to allocate resources to intercept illegal trade. This framework will then be applied to some networks motivated by data.

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Hominid interbirth interval and evolution of paternal care

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Unlike any great apes, humans have expanded into a wide variety of habitats during the course of evolution, beginning with the transition by australopithecines from forest to savanna habitation. Novel environments are likely to have imposed hominids a demographic challenge due to such factors as higher predation risk and scarcer food resources. In fact, recent studies have found a paucity of older relative to younger adults in hominid fossil remains, indicating considerably high adult mortality in australopithecines, early *Homo*, and Neanderthals. It is not clear to date why only human ancestors among all hominoid species could survive in these harsh environments. In this talk we explore the possibility that hominids had shorter interbirth intervals to enhance fertility than the extant apes. To infer interbirth intervals in fossil hominids, we introduce the notion of the critical interbirth interval, or the threshold length of birth spacing above which a population is expected to go to extinction. We develop a new method to obtain the critical interbirth intervals of hominids based on the observed ratios of older adults to all adults in fossil samples. Our analysis shows that the critical interbirth intervals of australopithecines, early *Homo*, and Neanderthals are significantly shorter than the observed interbirth intervals of extant great apes. This result suggests that the child care burden of hominid mother was reduced by other group members, including males. In fact, small canine of early hominids may indicate increasing importance of male provisioning, relative to male-male aggression, for males to gain higher reproductive success. To discuss evolutionary causes of these hominid features, we develop a mathematical model to obtain the condition for paternal care to evolve.

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The show-off hypothesis: the evolution of large-game hunting, and signalling like peacocks

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Large-game hunting in human hunter-gatherers is a counter-intuitive behaviour. Despite low daily success rates and large proportions of sharing, hunter-gatherers invest in large-game hunting over the less-wasteful strategy of small-game hunting. Where investment in small-game hunting could

provide a more reliable and consistent source of direct benefit to one's offspring, large-game hunting is more ecologically and environmentally dependent, and is a source of benefit to all members of a society, being shared unbiased to the hunter himself. Hypotheses attempt to explain this as reciprocity or altruism, wherein a hunter will share meat obtained as an investment in future returns from receiving beneficiaries of that meat. However, observations show that there is no correlation between current success rates with future obtained goods from others. The Show-Off Hypothesis is an alternate explanation of the evolution of large-game hunting, stating that such hunting behaviours act as a costly signal of one's quality as a mate. Better hunters are deemed as better mates, and hence obtain more paternities in a society. We investigate this, considering the effect of societal status on the evolution of the strategy of large-game hunting. We develop and present a model that defines measures of hunting success and the survival benefit of care, in order to shed light on previously unquantified effects of status on strategic choice. Within this model, we demonstrate the effect of maladaptive competition on male hunting strategic choice, and provide measures of the trade-off that drives the behaviour of large-game hunting.

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Theoretical proofs of evolutionary stabilities in indirect reciprocity of private assessment

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Private assessment in indirect reciprocity is a natural assumption because individuals can assess others privately in this situation. However, only few studies have considered private assessment because of analytical difficulty that it present. Here, we develop an analytical method using solitary observation to solve private assessment in indirect reciprocity problem without any approximation. In this study, we formulate a model of solitary observation and calculate the replicator dynamics systems of five leading norms of indirect reciprocity. Our theoretical solution shows that indirect reciprocity in private assessment provides a different result to that in public assessment.

According to the existence proofs of cooperative evolutionarily stable (CES) points in the system, strict norms (stern judging and shunning) have no CES point in private assessment, while they do in public assessment. Image scoring does not change the system regardless of the assessment types because it does not use second-order information. In tolerant norms (simple standing and staying), the CES points move to co-existence of norms and unconditional cooperators. Surprisingly, although there is no central coercive assessment system in private assessment, the average cooperation rate is greater than that in public assessment. This is because private assessment gives unconditional cooperators a role because the unconditional cooperators can raise the cooperation level of the society.

Our results also show the three advantages of the staying norm in private assessment: a higher cooperation rate, easiness of invasion into defectors, and robustness to maintain cooperative evolutionarily stable situations. Our results are applicable to general social dilemmas in relation to private information. Under some dilemmas, norms or assessment rules should be carefully chosen to enable cooperation to evolve.

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Campaigning to reduce ivory demand – is it cost effective?

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Illegal exploitation of wildlife is one of the biggest threats to biodiversity, affecting over 2,000 species. Traditionally, actions to reduce poaching have focussed on increasing the efficacy and capacity of law enforcement. However, recently, non-governmental agencies (NGOs) are heavily investing in alternative interventions to reduce consumer demand for poached wildlife products. But which action is more efficient, policing or demand reduction? Using elephant poaching for ivory as a case study, and a simple open-access harvest model, we show that demand reduction interventions need to reduce ivory price by roughly 29% to be more cost-effective than investing in the police. We use an analytic derivation to show that this threshold is robust to several types of uncertainty but sensitive to specific socio-economic factors. The calculations can provide context for stakeholder engagement so that monitoring of ivory price can better inform decisions for protecting elephants from poaching.

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Centralization in self-organized reference networks

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When one makes his/her decision, he/she often refers to others' opinions. We describe this situation by a network model with the nodes representing individuals and the links representing references between them. Our question is how people's reference structure self-organizes, when each individual tries to provide correct answers by referring to more accurate agents.

To answer these questions, we constructed an adaptive network model. In the model, in each iteration round, each agent makes a decision sequentially on a given problem by the majority vote among one's and his/her neighbors' opinions. Since each agent makes decision by the majority vote, his/her probability to find a correct answer by oneself, which we call his/her "ability", is different from his/her actual probability of finding a correct answer by referring to others, which we call his/her "performance". After the correct answer to a given problem is announced, each agent then rewires his/her links according to the performance of the linked individuals. The rewiring rule is as follows; each individual monitors his/her neighbors' performance and breaks the link if the neighbor's performance becomes worse than a preset threshold. We assume that all agents adopt the same threshold. Therefore the value of the preset threshold represents the severity of the society. We also assume that individuals vary in their ability.

In the self-organized reference network, we observed the strong centralization of reference, in which the number of one's followers increases more than linearly with his/her ability. Counter-intuitively, this tendency was stronger when the rewiring threshold was set lower (when they are more generous to their referents). The mean performance of each agent in the self-organized network was higher compared with random networks or the case of independent decision-making. However, the proportion of agents who give correct answers, which we call "group performance", fluctuated more in the self-organized network. To sum up, in the self-organized network, though the strong centralization of reference towards high ability agents leads to high performance of each agent on average,

it also leads to a heightened risk of a temporal crash in group performance. By analytical calculations, we have confirmed that the performance-monitoring process assumed in our model yields the strong centralization of reference in the self-organized reference network.

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Looking beyond the wavelength: exploring the impacts of electrophysiological variability on rotor-driven re-entries using emulation

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Variability in electrophysiological properties, between different cells in a given heart and between the hearts of different members in a population, has a profound impact on deciding both the susceptibility to dangerous arrhythmias and the success or failure of anti-arrhythmic treatments. This variability also complicates the interpretation of both experimental and clinical data, and the predictions of *in silico* models. A key biomarker in the understanding of arrhythmias is the wavelength of excitation fronts, a measure of how much tissue remains refractory in the wake of an excitation impulse. However, this tissue-level biomarker is found to be unable to predict the susceptibility to wavebreaks that trigger fibrillation. It is therefore important to consider variability in underlying cell-level properties more directly. Using a novel combination of supervised learning and emulation, we are able to greatly reduce the computational costs involved with exploring variability in large numbers of parameters, hence identifying how differences in these properties impact on some key aspects of rotor-driven re-entries, including risk factors for the devolution into fibrillation.

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Model of adipocytes size distribution

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Adipose tissue and adipocytes play a central role in the pathogenesis of metabolic diseases related to obesity. Size of fat cells depends on the balance of synthesis and mobilization of lipids and can undergo important variations throughout the life of the organism. These variations usually occur when storing and releasing lipids according to energy demand. This energy is stored as lipid droplets in their cytoplasm therefore adipocytes can adapt their size according to the lipid amount to be stored. Adipocyte size variation can reach one order of magnitude inside the same organism which is unique among cells. A striking feature in adipocytes size distribution is the lack of characteristic size since typical size distribution are bimodal. Since energy can be stored and retrieved and adipocytes are

responsible for these lipid fluxes, we proposed a model of size-dependent lipid fluxes that exhibits bimodal equilibria with generic conditions. This model is a non-linear transport equation structured by the size of adipocytes and we provide a dedicated stable numerical scheme solver able to capture the singular behaviour of solutions as concentration to Dirac masses. Using this solver, we are able to infer parameters related to lipid fluxes from size distribution. Performing recurrent surgical biopsies on rats, we measured the evolution of adipose cell size distribution for the same individual throughout the duration of feeding/refeeding experiments and use this data to assess fluxes parameters variations throughout the experiment.

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Multiscale adaptive analysis of circadian rhythms in the study of acute insomnia

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Circadian analysis is becoming increasingly important as a diagnostic tool to quantify deviations from regularity in circadian cycles. Circadian rhythms become less dominant and less regular with ageing and disease. It has been hypothesized that insomnia might be related to alterations, albeit small, in circadian and ultradian rhythms, but this topic remains an open problem. In this work, we propose a novel data-adaptive technique, singular spectrum analysis (SSA), to investigate in a model-free way quasiperiodic components and noise fluctuations in time series data. SSA was applied to one-week continuous actigraphy data in young adults with acute insomnia and healthy age-matched controls [1]. The findings suggest a small but significant delay in circadian components in the subjects with acute insomnia. The ultradian components follow a fractal $1/f$ power law for controls, however for individuals with acute insomnia this power law breaks down due to an increased variability at the 90min time scale. This is reminiscent of Kleitman's basic rest-activity (BRAC) cycles. It indicates that for healthy sleepers attention and activity can be sustained at time scale required by circumstances, while for individuals with acute insomnia this capacity may be impaired and they need to rest or switch activities in order to stay focused. Traditional methods of circadian rhythm analysis are unable to detect the more subtle effects of day-to-day variability and ultradian rhythm fragmentation at the specific 90min time scale.

[1] R Fossion, AL Rivera, JC Toledo-Roy, J Ellis and M Angelova. Multiscale adaptive analysis of circadian rhythms and intradaily variability: Application to actigraphy time series in acute insomnia subjects. *PLOS One*, 12(7): e0181762 (2017).

Human physiology / 300

Mathematical modelling for pacemaker-neuron-dependent molecular rhythm alteration by *Drosophila* clock mutant

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In *Drosophila*, circadian (~24h) behaviour is regulated by about 150 pacemaker neurons. To generate and maintain 24h rhythm, circadian gene expression in each pacemaker neurons is driven by transcriptional-translational feedback loop (TTFL). In TTFL of *Drosophila*, dCLOCK-CYCLE (dCLK-CYC) binds to the E-box (CACGTG) and activates the expression of period (*per*) and timeless (*tim*). Translated PER and TIM proteins repress their own transcription by removing dCLK-CYC dimer from the E-box. Interestingly, dCLK-Δ, which is a mutant of dCLK deleted amino acids (AA) 657-707 region and has impaired binding with PER, induces different effect on molecular rhythms depending on pacemaker neurons. For oscillation of PER, amplitude is largely reduced in ventral lateral neurons (LNvs), but not in dorsal neurons (DNs). However, how dCLK-Δ/CYC controlled TTFL operates differently in pacemaker neurons is unclear. To investigate this unexpected phenomenon, we established the mathematical model for the TTFL in *Drosophila* and predicted that pacemaker-neuron-dependent alteration of the molecular clockwork is caused by the difference of molecular composites between LNvs and DNs. This is confirmed by the follow up experiment. This work shows that clockworks at the molecular level have a critical role for specific functions of each pacemaker neurons.

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Numerical study of airway smooth muscle and airway wall coupled dynamics.

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Asthma is fundamentally a disease of airway constriction. Due to a variety of experimental challenges, the dynamics of airways are poorly understood. Of specific interest is the narrowing of the airway due to forces produced by the airway smooth muscle (ASM) wrapped around each airway. The interaction between the muscle and the airway wall is crucial for the airway constriction which occurs during an asthma attack. While crossbridge theory is a well-studied representation of complex smooth muscle dynamics, and these dynamics can be coupled to the airway wall, this comes at significant computational cost, even for isolated airways. Because many phenomena of interest in pulmonary physiology cannot be adequately understood by studying isolated airways, this presents a significant limitation. We present results associated with the development of an approximated method (distribution moment approximation) which provides orders of magnitude reduction in computational complexity whilst retaining rich ASM dynamics. This method is then used to model physiological processes such as airway contraction, bronchodilatory effect of a deep inspiration and preliminary results associated with heterogeneity of branched airways.

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Parameterizing continuum models of heat transfer in heterogeneous living skin using experimental data

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In this presentation we consider a recent experimental dataset describing heat conduction in living porcine tissues. This novel dataset is important because porcine skin is similar to human skin, and improving our understanding of heat conduction in human skin is directly relevant to understanding burn injuries, which are common, painful and can require expensive treatments. A key feature of skin is that it is layered, with different thermal properties in different layers. Since the experimental dataset involves heat conduction in living tissues of anesthetized animals, an important experimental restriction is that the temperature within the skin is only measured at one location within the layered skin. Our aim is to determine whether this data is sufficient to infer the heat conduction parameters in layered skin, and we use a simplified two-layer model of heat conduction to mimic the experimental dataset. Using synthetic data at one location in the two-layer model, we explore whether it is possible to infer values of the thermal diffusivity in both layers. After this initial exploration, we then examine how our ability to infer the thermal diffusivities changes when we vary the location at which the experimental data is recorded, and in the hypothetical situation where we monitor two locations. Overall, we find that our ability to parameterize a model of heterogeneous heat conduction with limited experimental data is extremely sensitive to the location where data is collected, and our modelling results can be used to provide guidance about future experimental designs.

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Grab Your Glasses! Modelling Cancer Immunology in 3D

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Immune responses to cancer-including innate responses and immunotherapy-involve complex biochemical and biomechanical interactions between tumour cells and many types of immune cells. To date, most modelling has not focused on the spatial and mechanical effects of these interactions. In this talk, we will adapt PhysiCell (an open source platform for 3-D multicellular systems biology [1]) to simulate individual immune cells as they respond to tumour-secreted immunostimulatory signals, adhere to cells, test immunogenicity, and induce apoptosis before repeating their search for new immunogenic targets. We will examine the key roles played by random motility and spatial geometry in the success or failure of an immune response. We will show ongoing work to bridge molecular and multicellular systems biology in 3-D multiscale simulations (e.g., [2]). Lastly, we will discuss and demonstrate the potential for high-throughput multicellular systems biology, where large parameter investigations can be run on supercomputers to efficiently explore 3-D multicellular dynamics under many sets of hypotheses [3], with examples in cancer immunology. With HPC-deployed versions of PhysiCell, we can complete a year's worth of mechanistic computational investigations in a little over a day. In the future, we believe that high-throughput mathematical model investigations will help drive biological discovery and even engineering of the immune system and other complex multicellular systems.

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[2] Letort *et al.*, "PhysiBoSS: a multi-scale agent based modelling framework integrating physical dimension and cell signalling," bioRxiv 267070 (2018), <https://doi.org/10.1101/267070>

[3] Ozik *et al.*, "High-throughput cancer hypothesis testing with an integrated PhysiCell-EMES workflow", bioRxiv 196709 (2017), <https://doi.org/10.1101/196709>

Immunobiology and infection subgroup / 50

The geometry of leukemic proliferation

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Complex protein interaction networks complicate the understanding of what most promotes the rate of cancer progression. High dimensional data provides new insights into possible mechanisms for the proliferative nature of aggressive cancers, but these datasets often require fresh techniques and ideas for exploration and analysis. In this talk, we consider expression levels of tens of proteins that were recorded in individual cells from acute myeloid leukemia (AML) patients via mass cytometry. After identifying immune cell subpopulations in this data using an established clustering method, we use topological data analysis to search for subpopulations that are most actively proliferating. To conduct the search within these subpopulations, we build on the differential geometric perspective that led to our recent statistic for testing aggregate differences in protein correlations between patients with different subtypes of AML.

Immunobiology and infection subgroup / 405

Same-same but different: how heterogeneity within tumours can derail immunotherapy!

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Cancer presents one of the largest problems in our modern society. Understanding even the smallest aspect of this disease is immensely challenging due to its heterogeneous nature, a characteristic we term the ‘same-same but different’ nature of cancer. Heterogeneity can exist across tumour types depending on what stage the tumour is at or what organ the tumour exists in. There are many contributing factors that can be affected by differences between cancers, e.g.: tumour growth rate, tumour cell S-phase length, vascularisation and many more. The effects of these differences on the outcome of cancer therapies are still not fully understood and present a hurdle to modern cancer therapies. To add to the complexity of this problem, within tumours themselves, there is an array of ‘same-same but different’ characteristics that tumours can have, such as structure, pressure and anti-viral immune responses. Using mathematical modelling, we investigate the effect of tumour heterogeneity on the outcome of virotherapy and immunotherapy. Using distributed delay models and agent-based modelling we unravel the layers of tumour heterogeneity and answer two key questions “why does heterogeneity within a tumour derail immunotherapy?” and “how can we overcome this obstacle?” Optimisation of current experimental data helps us tie down parameter values and suggest with some level of confidence how treatments, such as immunotherapy, can be improved to overcome the challenges presented by dissimilarities within and across tumour types.

Immunobiology and infection subgroup / 446

Flu ACHOO! Modelling the immune response to influenza-bacterial coinfection

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Influenza A virus (IAV) infections are often complicated by bacterial pathogens like *Streptococcus pneumoniae* (SP, pneumococcus), which have accounted for 40-95% of IAV-associated mortality. IAV-SP coinfection is characterized by rapid, uncontrolled bacterial growth, a rebound in viral titers, and a robust inflammatory response. Several factors contribute to influenza-pneumococcal pathogenicity, including aberrant immune responses, tissue destruction, and pathogen strain and dose. To determine the contribution, regulation, and time-scales of different mechanisms, we analyze infection kinetics with mathematical models then experimentally validate our model predictions. Through this model-experiment exchange, we have identified how virus induced alveolar macrophage (AM) depletion dictates bacterial establishment and initial growth kinetics, and that bacteria enhance virus replication efficiency by blocking interferon (IFN) signalling. Because additional mechanisms may contribute to the development of pneumonia in coinfecting animal, we infected mice with IAV then SP at different times post-influenza and simultaneously measured numerous variables. Modelling these data suggests that new infections contribute to the viral rebound, that suppressed T cell responses and exacerbated IFN responses have little impact, that the increased AM depletion is bacterial mediated. Collectively, our models and data provide insight into the mechanisms of IAV-SP coinfection, demonstrate the accuracy and predictive power of theoretical models, and highlight the importance of validating model predictions.

In-host infections, HIV, immunity / 335

Bistable dynamics in a model of SIV infection with antibody response

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Experiments in rhesus macaques have shown that for simian immunodeficiency virus the size of the viral inoculum and the infection stage of the donor animal alter the likelihood of establishment of infection. In this study, we postulate a role for the host and donor antibodies in explaining the dependence of infectiousness on donor infection stage. The resulting mathematical model exhibits bistable dynamics, with viral clearance and persistence dependent on initial conditions. We fit the model to temporal virus data using a censored data approach for measurements below the limit of detection, and make predictions about the minimal viral load in the inoculum required for persistent infection.

In-host infections, HIV, immunity / 77

Modelling latency using a distribution of life spans among infected cells

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Understanding the mechanisms of HIV latency is important in the development of strategies for managing infection. Time from infection until production of virus has been shown to vary among infected cells, hence challenging the dichotomous assumption that cells are either latent or productively infected at time of infection. In this paper, we will explore the implications of an alternative hypothesis that rates of activation follow a probability distribution, of which latency is just an extreme of this spectrum. We show the emerging dynamics from this mathematical model and test its ability to explain features of reservoir formation and decay observed in SIV data. Analysis of SIV DNA levels in macaques that start treatment at different times shows that the decay rates of cells are statistically different in early and late initiation of treatment. Modelling suggests that data can be explained by a spectrum of reactivation rates of infected cells.

In-host infections, HIV, immunity / 473

Cell fate decision in *Chlamydia Trachomatis*

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Chlamydia trachomatis is the most common cause of bacterial sexually transmitted infection. It can also infect the eyes and is a major cause of blindness in many developing countries. During the infection of a mammalian host, *Chlamydia* must decide when to proliferate and when to convert into a differentiated form, since the differentiated form is the only form to survive outside the host but cannot reproduce. We study the question of *Chlamydia* cell fate regulation using experimental data as well as stochastic mathematical modelling.

In-host infections, HIV, immunity / 365

Unravelling the role of IL-10 in the development and function of the TB Granuloma

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Tuberculosis (TB), a deadly infectious disease caused by the bacterium *Mycobacterium tuberculosis* (Mtb). The disease is characterized by the development of granulomas consisting of immune cells that form a cluster around the bacteria to limit bacterial growth and disease outcomes. Control of the TB epidemic is limited by a complicated drug regimen, development of antibiotic resistance, and the lack of an effective vaccine against infection and disease.

There are a range of pro- and anti-inflammatory molecules associated with Mtb infection and it has been shown that depletion of a specific anti-inflammatory molecule, namely IL-10, is associated with improved vaccine efficacy in mice. However, there are conflicting results in both mice and monkeys as to the effects of IL-10 depletion on disease, with some studies showing that the depletion of anti-inflammatory factors improves disease outcome and others demonstrating that this depletion causes more severe disease. In previously published modelling studies, we suggest that depleting IL-10 can increase the probability that a granuloma is cleared in non-human primates (NHPs).

Using GranSim, our previously published hybrid, multiscale, agent-based model of granuloma formation following Mtb infection, we explore the role of IL-10, on granuloma development and function. In this exploratory study, we simulate the depletion of IL-10 from two discrete time points. The first time point coincides with the infection time of Mtb, and allows us to examine the role of IL-10 in granuloma formation. Elucidating the mechanisms by which IL-10 affects granuloma formation allows us explore whether the improvement in vaccine efficacy that has been identified in mice can also be observed in our model. The second time point is at 200 days post infection when a stable granuloma is already established to allow us to identify the mechanisms by which IL-10 is acting upon granuloma function and maintenance. Understanding the effect of IL-10 depletion on established TB granulomas is important to identify new therapeutic pathways for this disease.

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Lifelong CMV infection minimises age-related decline in the diversity of T cells recruited into the immune response to another infection

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The elderly population is particularly susceptible to infectious diseases, such as influenza, as evidenced by increased occurrence and severity of infection, and reduced vaccine efficacy. Studies suggest an association between persistent cytomegalovirus (CMV) infection and deficiencies of the aged immune system. CMV is a common herpes virus that infects up to 85% of the population aged 40 years or over. Healthy individuals rarely experience symptoms after the initial CMV infection. However, the virus remains in the body in an inactive state and constant surveillance by the immune system is required to detect and suppress reactivation of the virus. It is unclear whether this lifelong burden on the immune system to control persistent CMV infection plays a causal role in age-related compromise of the immune system to fight infections and respond to vaccines.

The effect of age on the immune system is multifactorial. One factor is a decline in the diversity of CD8+ “killer” T cells recruited by the immune system to fight a particular infection. In this study we investigated whether the presence of lifelong CMV infection impacts the diversity of T cells responding to another infection in aged mice. The diversity of T cells responding to infection was assessed using single-cell Sanger sequencing and bioinformatics analysis of the T cell receptors, which are expressed on the surface of individual T cells to enable the detection of virus. Various features of the T cell receptors, including diversity, gene usage, sequence length, and conserved patterns of amino acid usage were quantitatively compared between three groups of mice: young adult and old adult mice with no CMV infection and old mice with lifelong CMV infection. T cell diversity was quantified using ecological measures of diversity and rarefaction to standardize for differences in sample sizes. Our results demonstrate that, in the absence of persistent CMV infection, T cell responses in old mice were significantly less diverse than in young adult mice. In contrast, T cell diversity was maintained in the old mice with CMV infection and we did not observe the age-related narrowing of the T cell population that occurred in the absence of persistent CMV infection. Next-generation sequencing of the broader T cell populations that have not previously encountered infection showed similar T cell diversity in all three groups of mice, including the presence of T cell receptors that were recruited into the immune response in CMV-infected old mice but not in old mice without CMV infection.

These results suggest that lifelong CMV infection may actually improve T cell immunity in later life by broadening the diversity of T cells that can be effectively recruited and/or maintained in immune responses to other infections. Furthermore, these results challenge the paradigm that CMV has a negative impact on the ageing immune system.

In-host infections, HIV, immunity / 322

Theoretical study of interaction between allergy and intestinal microbiome

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Recent studies show that human immune system interacts with intestinal microbiome. A certain group of intestinal bacteria is known to be possible suppressor of undesirable immune response [1]. They produce short chain fatty acid such as butyrate and induce regulatory T cells [1]. Regulatory T cells are suppressor of exaggerated immune responses [2]. Therefore, collapse of the ecological balance of intestinal microbiome may cause dysregulation of immune system. On the other hand, mutant mice with regulatory T cells that have limited diversity of T cell receptor repertoire cause inflammation to commensal intestinal microbiome driven by T helper cells [3], suggesting that immune cells develop hypersensitive response to commensal microbiome and that regulatory T cells suppress the reactions.

This suggests us that intervention targeting intestinal microbiome may provide a novel strategy for treatment of allergic symptoms. In this talk, we develop a simple mathematical model that describes interaction between intestinal microbiome and immune system. We consider dynamics of T helper cells (trigger of allergic response), regulatory T cells (suppressor of allergy), and intestinal microbiome. Differentiation process of these two types of T cells is described as a model of immune system, the structure of which was developed in our previous study [4].

Analysis shows that the model has results of three different types differing in stable steady states: (1) the case with a single stable positive steady state representing “healthy condition”, (2) the case with a single stable steady state representing “allergic condition”, and (3) the case with two stable steady states, representing “healthy” and “allergic” conditions, respectively. Steady states representing healthy condition has a low level of helper T cells, a high level of regulatory T cells, and bacteria; whilst those representing allergic condition has opposite features (high helper T cells, low regulatory T cells and bacteria). Considering these three different situations, now we have two strategies for allergy treatment. The first strategy is to eliminate steady state which corresponds to allergy, by realizing the condition for case (1). We derived a formula for the absence of allergic state. The second strategy is to reduce the abundance of helper T cells at the steady state. We tested bacteria-related parameters for their effectiveness in suppressing the level of helper T cells. This study is the first attempt in modelling association between intestinal microbiome and immune system and in finding out a therapy method for allergy by intervention of intestinal microbiome.

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In-host, cell cycle & differentiation / 261

A transcriptional regulatory network of cell type specific gene expression in hematopoiesis

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During differentiation process, cell type specific gene expression pattern is established by orchestrate regulatory network of transcription factors (TFs). Resolving the structure of the transcriptional regulatory network (TRN) is promising way to understand the detailed mechanism of cell differentiation.

Here I estimate a transcriptional regulatory network determining the cell type specific gene expression pattern in hematopoiesis obtained from public database (GEO accession number GSE60101)[1]. Transcription factors upregulated in at least one cell type through hematopoiesis are identified as cell type specific transcription factors. It is simply assumed that the expression of the transcription factor is regulated by transcription factors of those binding motifs are enriched in its promoter region. A transcriptional regulatory network of cell type specific gene expression is estimated based on the expression profile and distribution of enriched transcription factor binding motifs in the promoter regions. The network is represented as a directional graph. And the structure of the network is analyzed based on graph theory.

Branching process where two different cell types differentiate from one progenitor through hematopoiesis is especially focused in this study. Transcriptional regulatory networks of Common Myeloid Progenitor (CMP) and Common Lymphoid Progenitor (CLP) specific gene expressions are constructed. To compare with these regulatory networks, a regulatory network of hematopoietic stem cell is also constructed as a pluripotent cell.

Through the network analysis it is clarified that the modular structure in the transcriptional regulatory network is developed through cell differentiation process. In CMP network TFs mainly regulated by Cebp family member is obviously clustered. Average expression levels of TFs in this Cebp cluster gradually increase through granulocyte differentiation. It is suggested that these TFs in Cebp cluster are myeloid lineage signature TFs. On the other hand, TFs mainly regulated by Lef1 are clustered in CLP network. Average expression levels of Lef1 cluster TFs increase in lymphoid lineage cells such as T cell and B cell. The network analysis in this study suggests that development of the modular structures composed of specific cell lineage signature TFs are critical mechanism determining cell fate.

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In-host, cell cycle & differentiation / 63

Continuum mathematical models for cell migration incorporating cell cycle dynamics

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Fluorescent ubiquitination-based cell cycle indicator, also known as FUCCI, allows the visualisation of the G1 and S/G2/M cell cycle phases of individual cells. FUCCI consists of two fluorescent probes, so that cells in the G1 phase fluoresce red and cells in the S/G2/M phase fluoresce green. FUCCI

reveals real-time information about cell cycle dynamics of individual cells, and can be used to explore how the cell cycle relates to the location of individual cells, local cell density, and different cellular microenvironments. In particular, FUCCI is used in experimental studies examining cell migration, such as malignant invasion and wound healing. Here we present new mathematical models which can describe cell migration and cell cycle dynamics as indicated by FUCCI. The *fundamental* model describes the two cell cycle phases, G1 and S/G2/M, which FUCCI directly labels. The *extended* model includes a third phase, early S, which FUCCI indirectly labels. We present experimental data from scratch assays using FUCCI-transduced melanoma cells, and show that the predictions of spatial and temporal patterns of cell density in the experiments can be described by the fundamental model. We obtain numerical solutions of both the fundamental and extended models, which can take the form of travelling waves. These solutions are mathematically interesting because they are a combination of moving wavefronts and moving pulses. We derive and confirm a simple analytical expression for the minimum wave speed, as well as exploring how the wave speed depends on the spatial decay rate of the initial condition.

In-host, cell cycle & differentiation / 241

Modelling of robust genetic switch with a single input, based on a serine integrase-controlled toggle switch

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Binary genetic switches are widely used in synthetic biology for switching between two expression states, ON and OFF. In particular, single input switches, which alternate between ON and OFF in response to the same input signals, are the key elements of counting devices which count the occurrence of a repeated intracellular or extracellular signal. Most existing DNA switches require two inputs, and no single-input switch capable of robust switching between two states has been developed so far. Here we use mathematical modelling to design such a switch by combining two double-input DNA switches: a transcriptional toggle switch (TTS) and a DNA inversion switch. The TTS switches between expression of two transcriptional repressors, mutually inhibiting each other. The DNA inversion switch is based on recombination by a serine integrase, inverting a DNA segment located between two attachment sites. Integrase reverses its directionality in the presence of a recombination directionality factor (RDF); therefore the alternate induction of integrase with or without RDF results in flipping of the DNA segment. In the design of our one-input switch the TTS ensures bistability, while the DNA inversion switch provides a single-input control by flipping the DNA segment with an inducible promoter. The model predicts that the combined bistability of the TTS and unidirectionality of DNA recombination ensure nearly 100% efficiency of switching between ON and OFF states in response to repeated pulses of inducer. The switch is predicted to be robust to parameter perturbations and molecular noise, making it a promising candidate for further use as a basic element of counting devices.

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Quantitative assessment of the dynamics of soluble form of DNAM-1 (CD226) in human serum explains the mechanism of acute Graft Versus Host Disease (GVHD).

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Acute graft-versus-host disease (aGVHD) is the major complication of Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT). A lot of previous studies showed that the importance of DNAM-1(CD226) which is expressed on CD4+ T cells, CD8+ T cells, natural killer (NK) cells, and monocytes. Therefore, DNAM-1 has been considered as essential molecule of developing aGVHD *in vitro* and *vivo* [1], [2]. But understanding the mechanism of aGVHD in human body is not understood well since few clinical trials related to the mechanism of aGVHD were performed. Recently, Kanaya *et al.* [3] focused on the soluble form of DNAM-1 (sDNAM-1) and collected the data which were from the subjects who received the transplantation. A form of the data set is time course therefore each subject has several observations by each time point. Despite of the time course data set, they just focus on the maximum value of the observation i.e. they didn't assess the dynamics of soluble DNAM-1. Therefore, they couldn't explain the connection between the dynamics of sDNAM-1 and developing aGVHD well. So then, we analyzed this data set by considering the dynamics of sDNAM-1. In our research, we made the hypothesis of mechanism of aGVHD and proved it by applying mathematical model and computational simulation to this data set. These results suggest that there exist 3 types of DNAM-1 after transplantation in the subject's body. The 1st type of DNAM-1 is released temporally and the 2nd types of DNAM-1 is released constantly. Those are from donor cells. On the other hand, 3rd types of DNAM-1 is residual one in the recipient body which is released from recipient cells. In addition, we proved quantitatively that the more 1st type of DNAM-1 exist in the human body after transplantation, the more the subjects tend to develop aGVHD. From the several previous researches and this research, we conclude that those cells which release DNAM-1 temporarily can be considered as allo reactive T cells. Therefore, allo reactive T cells which expresses DNAM-1 can be treatment target for aGVHD.

[1] T. Nabekura *et al.*, "Critical role of DNAX accessory molecule-1 (DNAM-1) in the development of acute graft-versus-host disease in mice," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 107, no. 43, pp. 18593–8, Oct. 2010.

[2] M. Koyama *et al.*, "Promoting regulation via the inhibition of DNAM-1 after transplantation," *Blood*, vol. 121, no. 17, pp. 3511–20, Apr. 2013.

[3] M. Kanaya *et al.*, "Soluble DNAM-1, as a predictive biomarker for acute Graft-Versus-Host disease," *PLoS One*, vol. 11, no. 6, pp. 1–12, 2016.

In-host, cell cycle & differentiation / 112

Modelling cell proliferation times

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Typically, discrete stochastic models of cell proliferation use a rate to determine whether or not a cell proliferates at a particular time, producing an exponential distribution for the time between proliferation events. Actual experiments, however, suggest that cells actually have a Gaussian distribution in their time to proliferate, with a relatively small standard deviation. This talk will discuss the similarities and differences in the group behaviour depending on the proliferation model: both the surprising match after a single time step, and the large differences as simulations progress.

Interdisciplinary approaches in developmental biology / 78

Modelling the migration of astrocytes during retinal development

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Retinal vasculature is essential for adequate oxygen supply to the inner layers of the retina, the light sensitive tissue in the eye. In embryonic development, formation of the retinal vasculature via angiogenesis is critically dependent on prior establishment of a mesh of astrocytes, which are a type of brain glial cell. Astrocytes emerge from the optic nerve head and then migrate over the retinal surface as a proliferating cell population in a radially symmetric manner. Astrocytes begin as stem cells, termed astrocyte precursor cells (APCs), then transition to immature perinatal astrocytes (IPAs) which eventually transition to mature astrocytes. We develop a partial differential equation model describing the migration of astrocytes where APCs and IPAs are represented as two subpopulations. Numerical simulations are compared to experimental data to assist in elucidating the mechanisms responsible for the distribution of astrocytes.

Interdisciplinary approaches in developmental biology / 104

A quantitative and systems approach to vertebrate forebrain and heart morphogenesis

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Understanding how 3D organ morphology is achieved during development is one of the ultimate goals in biology. This is important not only for pure scientific interests but also for potential medical applications for controlling and designing functional organs. To achieve these goals, it is essential to clarify the quantitative relationships between microscopic molecular/cellular activities and organ-level tissue deformation dynamics. While the former has been studied for several decades, the latter - macroscopic geometrical information about physical tissue deformation - has been lacking. One reason for this lack of information is the difficulty in measurement at high resolution. We recently proposed a Bayesian method to precisely reconstruct global deformation patterns for three-dimensional morphogenesis of curved epithelial sheets using positional data from sparsely-labeled cells with limited resolution [1]. The applications of the method to early development of chick forebrain and heart revealed that globally aligned anisotropic deformation (i.e., biased tissue stretching), rather than local area growth, is the predominant morphogenetic mechanism in both cases (specifically, for optic vesicle formation and C-looping, respectively) [2]. Comparing the reconstructed tissue deformation patterns and cellular behaviours, we quantitatively revealed the contributions of each cellular process (e.g., division, size/shape change, and rearrangement) to the anisotropic tissue deformation. In this talk, we would also like to introduce our attempt to build continuum mechanical models to reproduce observed morphologies and deformation patterns.

[1] Morishita *et al.*, Nat. Commun., 2017

[2] Kawahira *et al.*, under review

Interdisciplinary approaches in developmental biology / 387

Collective cell migration in an open channel

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The collective migration of cells during embryogenesis is key to the development of vertebrates, and improper migration can lead to severe developmental diseases and deformities. As a simple model for such cell migration we study the particle based Vicsek model in an open channel geometry where cells continuously enter and leave the domain. This results in two distinct types of motion – one corresponds to desired, well-ordered migration, while the other corresponds to disordered migration. We characterise the different types of collective behaviour and propose a theoretical description to determine the conditions for coherent collective cell migration.

Interdisciplinary approaches in developmental biology / 418

Modularity, criticality and evolvability of a developmental gene regulatory network

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Insects use two main modes of segment determination during development: the ancestral short-germband mode (eg. *Gryllus bimaculatus*) where new segments are added sequentially, and the more derived long-germband mode (eg. *Drosophila melanogaster*), where all segments are determined simultaneously. In dipteran insects (flies, midges and mosquitoes), which use the long-germband mode of segmentation, the gap genes are activated by maternal gradients and cross-regulate each other to form the first zygotic layer of regulation in the segmentation gene hierarchy. We reverse-engineered a dynamical model of the gap genes in *D. melanogaster* from quantitative spatio-temporal expression data and used it to characterise the dynamics of gap gene pattern formation along the embryo trunk. We used tools and concepts from dynamical systems theory, coupled with a newly developed methodology designed specifically to address the effect of maternal gradient dynamics in the patterning process. This approach showed that two distinct dynamical regimes govern anterior and posterior trunk patterning. Stationary domain boundaries in the anterior rely on multi-stability. In contrast, the observed anterior shifts of posterior gap gene domains can be explained as an emergent property of an underlying regulatory mechanism implementing a damped oscillator. We have identified a dual-function three-gene motif embedded in the gap gene regulatory network, which is sufficient to recover both anterior and posterior dynamical regimes. Which one drives gene expression in a given region depends on the gap genes involved. Interestingly, this sub-network - known as the AC/DC motif - can also sustain oscillations. Oscillations are not found in the gap gene system but are characteristic of short-germband segmentation, suggesting that both modes share much more than previously thought. Studying the evolution of the gap gene network as an evolving dynamical system will tell us how oscillations could have arisen or ceased, and this will help us understand how long-germband segmentation might have repeatedly and independently evolved from the ancestral short-germband mode.

Interdisciplinary approaches in developmental biology / 507

Three-dimensional excitable wave dynamics depend on the cell geometry in *Dictyotellium* cells

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Phosphatidylinositol (3,4,5)-trisphosphate (PtdInsP3) is known to propagate as waves on the plasma membrane and is related to the membrane protrusive activities in *Dictyostelium* and mammalian cells. While there have been a few attempts to study their three dimensional dynamics, most of these studies focused on the dynamics extracted in one dimensional sections along the membrane in a single focal plane. However, the relation between the dynamics and three-dimensional cell shape remain elusive due to the lack of signalling information on the remaining non-observed part of the membrane. Here, we show that PtdInsP3 wave dynamics are directly regulated by the three-dimensional geometry - size and shape - of the plasma membrane. By introducing an analysis method that extracts the three-dimensional spatiotemporal activities on the entire cell membrane, we show that PtdInsP3 waves self-regulate their dynamics within the confined membrane area leading to changes in speed, orientation and pattern evolution following the underlying excitability of the signal transduction system. Our findings emphasize the role of the membrane topology in reaction-diffusion driven biological systems and indicate the importance of the plasma membrane topology in other mammalian systems.

Interdisciplinary approaches in developmental biology / 84

Quantifying and modelling epithelial morphogenesis

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In the course of animal development, the shape of macroscopic tissues emerges from collective cell dynamics. The challenge faced by researchers in the field is to understand the mechanism by which morphogenetic processes of each individual cell (i.e., when, where, and how much individual cells grow, divide, move, and die) collectively lead to the development of a large tissue with its correct shape and size.

Answering this question requires a coarse-grained description and modelling of cell and tissue dynamics at an appropriate length scale. In a previous study, we developed coarse-grained measurement methods for stress and kinematic fields. These methods are now emerging as powerful tools used for exploring the mechanics of epithelial tissues. Given the advancement of experimental measurement methods, one can expect that a theoretical model for kinematics and kinetics in a deforming tissue, which can be compared with the experimentally observable fields, will further advance our understanding of the mechanical control of tissue morphogenesis.

Here, we present a new continuum model of epithelial mechanics. This model incorporates stress and deformation tensors, which can be compared with experimental data. Using this model, we elucidated dynamical behaviour underlying passive relaxation, active contraction-elongation, and tissue shear flow. This study provides an integrated scheme for the understanding of the orchestration of morphogenetic processes in individual cells to achieve epithelial tissue morphogenesis.

Interdisciplinary curriculum development at the interface of mathematics, life science, and computing: challenges and progress / 51

Zombies, foxes and murder: experiences in learning and teaching quantitative biology using technology

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Since the publication of the National Research Council's Report *BIO2010*, efforts have increased to better integrate mathematics and biology at the undergraduate level. Unfortunately, similar efforts to introduce quantitative biology at the secondary level have been seldom. This can lead to quantitative achievement mismatch in students from different secondary backgrounds. We believe that technology can be used in order to diminish this mismatch. Technology has become pervasive in the personal lives of secondary and undergraduate students, but some instructors are hesitant to incorporate technology into pedagogy. In this work, we review available resources for teaching quantitative biology with technology, and anecdotally explore the effectiveness of learning with and teaching with these resources.

Interdisciplinary curriculum development at the interface of mathematics, life science, and computing: challenges and progress / 75

Population modelling in an applied calculus class using spreadsheets

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In this talk I will describe a series of population modelling computer labs used in an applied calculus class. The labs showcase different types of population growth, including Fibonacci, exponential, and logistic. Exponential growth is revisited as a differential equation, which is approximated by discrete growth, that is, approximation via tangent lines, using different time intervals. In some semesters, students used the world population data to examine the issue of whether the population is growing exponentially or logistically. Each lab requires the students to use a spreadsheet program, such as Excel, giving students practice with this essential computer skill.

Interdisciplinary curriculum development at the interface of mathematics, life science, and computing: challenges and progress / 136

Coding in the classroom

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There are many benefits to incorporating coding into mathematics classrooms: students begin to think algorithmically about mathematics, students learn a transferable skill, and the courses can

include more real-world, data-driven problems. However, bringing programming into the math curriculum presents challenges. Success and difficulties of integrating programming into the liberal arts mathematics classroom will be presented. In particular, incorporating programming in conjunction with the development of an interdisciplinary biomathematics program at a liberal arts college will be discussed.

Interdisciplinary curriculum development at the interface of mathematics, life science, and computing: challenges and progress / 461

Assessing the “ID” Part of ID-STEM Learning

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Student progress in “interdisciplinary (ID) thinking” is remarkably resistant to many established means of evaluation. A sophisticated skill, such thinking does not fit well into old instruments, like timed exams. In contrast to discipline-specific skill sets, a student’s ability to view problems from multiple-disciplinary perspectives cannot be evaluated in terms of an objective standard, and, therefore, requires both pre- and post-assessment. We will discuss issues related to this matter, and will share potential strategies for effective assessment of student gains in ID thinking.

Interdisciplinary curriculum development at the interface of mathematics, life science, and computing: challenges and progress / 49

Teaching mathematical modelling in ecology: experiences from a new interdisciplinary course

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Although many of the most important academic problems lie at the interface of traditional disciplines, undergraduate students are rarely exposed to true interdisciplinary learning in their courses. Indeed, despite the necessity for mathematical and computational skills in modern biological and environmental research, most life science students lack any experience with higher-level mathematics or how to apply it. Here, I present experiences from a newly developed interdisciplinary Mathematical Modelling in Ecology course taught by myself (in the Department of Environmental and Ocean Sciences) and a colleague (Dr. Amanda Ruiz in the Department of Mathematics) at the University of San Diego (USD). In this course, both Environmental and Ocean Sciences majors and Mathematics majors and minors learned about how mathematical concepts can be applied to address ecological questions. This course used a novel “linked” design in which the two groups of students were enrolled in separate classes but that were offered at the same time; this allowed the two student groups to learn at different paces, but to sometimes be combined to facilitate peer learning and collaborative problem solving. In addition, each week there was a joint 3-hour lab, in which students from both classes worked together in groups on complex interdisciplinary assignments to address ecological questions using both mathematical and computational techniques. I will discuss both the successes and challenges from our first time teaching this course, both from a faculty perspective, and from end-of-the-semester student surveys. Lastly, I present potential future directions for this course and similar courses at other universities with the aim of further developing interdisciplinary curriculum at the interface of mathematics and biology.

Interdisciplinary curriculum development at the interface of mathematics, life science, and computing: challenges and progress / 164

Modelling with data in an introductory numerical methods course

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Modelling with real data in the classroom not only gives students a sense of why the mathematics matters, but it also gives them perspective on how messy the real world is and how we adapt our models to suit non-perfect data. We present a class activity and project for an introductory numerical methods course in which Calculus 1 and 2 are prerequisites. In the classroom we introduce curvature and a method for calculating curvature using discrete points. We then explore how we could use curvature to identify sinkholes given data from high resolution digital elevation models (DEMs). Outside of class, groups of students create codes in Matlab to calculate the curvature at each boundary point of some given depression. Each group then decides how to use these individual curvatures to determine whether a depression is a sinkhole. Once all projects are complete the students present their methods in class and test their codes on actual geological data. Although this project is geological in nature, it could be used with any application in which identification is based on roundness.

Internal flows in soft tissue tubes: Evo + Devo + Physio / 256

Multiscale modelling of saliva secretion

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The parotid salivary gland consists of groups of acinar cells all transporting water into a lumen with a complex branched structure. In addition, each acinar cell itself has a complex spatial structure, with heterogenous spatial distributions of the channels that control water transport. The goal of our model is to determine the relationships between structure and function, both at the level of individual acinar cells, and at the level of the entire salivary gland.

To answer this question we have constructed an anatomically accurate model, based on reconstruction of a z-series of optical slices through a group of acinar cells. Our model shows how the structure of each acinar cell is critical for an understanding of how water flow through each cell is controlled, and how the multicellular branching structure of the lumen can affect total fluid flow.

Internal flows in soft tissue tubes: Evo + Devo + Physio / 155

Assessing physical control mechanisms in lung branching morphogenesis

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We have developed several models of the physical control of branching morphogenesis in the lung, considering a variety of factors, including transport and mechanics. Simple models can explain complex phenomena, though how reasonable a model initially seems is not necessarily correlated with its ultimate explanatory power. In this talk, we will present a variety of models of branching morphogenesis, and compare their implications.

Internal flows in soft tissue tubes: Evo + Devo + Physio / 74

Optimal flow patterns in branching lymphatic vessels

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Understanding lymphatic development is clinically relevant in applications from the viability of embryos, to chronic inflammation, to cancer metastasis. I specifically quantify the branching structure of developing lymphatic vessels and numerically solve for the flow through these vessels. Branching in arterial development is understood to consistently follow Murray's Law, which states that the cube of the radius of a parent vessel is equal to the sum of the cubes of the radii of the daughter vessels, thus minimizing the cost and maintenance of fluid transport. I have found that an optimization law for lymphatic vessels is less straightforward. The derivation of Murray's Law includes several assumptions, such as vessels of constant diameter filled with a Newtonian fluid, fully developed and unidirectional flow, and long segments between junctions. Several of these necessary assumptions do not hold for lymphatic capillaries. The relationship between the parent and daughter vessels is upheld through a strictly additive rule, and the daughter vessels are smaller than would be predicted by the hypothesized radius-cubed law. The variability in vessel diameter and potential for bidirectional flow suggest a different optimization strategy based on the geometry and function of the system. In this presentation, the immersed boundary method is used to numerically solve the equations of fluid flow through branching vessels. The results are then used to test the assumptions of Murray's Law as well as several hypotheses regarding branching geometry.

Internal flows in soft tissue tubes: Evo + Devo + Physio / 468

Uncertainty analysis applied to model peristalsis to understand evolution

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Biologists are interested in functional performance based on complicated mechanical systems to understand how structures may have evolved. Since direct manipulation of these systems in an organism are not always possible, many functional systems are modelled using computational methods, such as computational fluid dynamics. These functional systems and their simplified models involve many parameters which may or may not affect the performance output of the system in strong

ways, in other words, the functional output often has varying sensitivity to each input parameter in the system. Therefore variation, both a natural consequence of development and the raw material on which natural selection operates, is difficult to quantify with typical methods on computational models, such as single parameter sweeps of simulations while other parameters are held constant. In this work, we apply existing uncertainty quantification methods on CFD models of a functional system to answer the question: how does variation in the input parameter space affect model output in a way similar to what natural selection would act upon? Through the use of generalized polynomial chaos and calculation of Sobol indices, we quantify the uncertainty on a model of circulatory flow using two methods of driving peristaltic motion (two opposing sine waves and a traveling pinch). Sensitivities of three input parameters are discussed: Womersley number, compression ratio (the percent occlusion of the tube during a compression), and compression frequency. Specific predictions about natural diversity are made based on sensitivities; those parameters that are very sensitive should be highly constrained versus those that are insensitive should exhibit high levels of diversification.

Mathematical and experimental approaches to understand immune response to infection / 513

Search times of T Cells in the liver

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The prevention of diseases such as malaria require certain T cells to find all pathogens in the liver within a certain period of time (e.g., within 48 hours, which is the time required for liver-stage development of parasites in rodent malaria). This motivates the fundamental question of how many T cells are required to ensure complete coverage of the liver within a specified time, to a high probability. After describing our existing results, we will present our current thoughts and approaches. Explanations will be given of how to model the liver sinusoids, how to implement fast simulations of T cell movement, and various possibilities for how to model the movement of T cells.

Mathematical and experimental approaches to understand immune response to infection / 308

Trajectory inference of HIV progression with microbiome data

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Information analysis of amplicon sequencing of fecal samples from HIV positive individuals suggested an enrichment of a particular bacterial species in the gut microbiota, as referred to dysbiosis. Although a sufficient number of samples has already accumulated for both HIV positive and negative subjects, time-series datasets are rarely available. Hence difficulty remains in tracing the compositional change of the gut microbiota during HIV infection.

In this presentation, we would like to introduce our ongoing research progress on the application of trajectory inference methods to construct a pseudo-trajectory that may imitate disease progression

of HIV infection. Our computational analysis suggested that enrichment of the *enterobacteriaceae* family may occur at the initial phase of HIV infection during which inflammatory responses would be facilitated in the gut. This finding is consistent with known observations for the enrichment of the *enterobacteriaceae* family in several inflammatory diseases.

Mathematical and experimental approaches to understand immune response to infection / 476

Imaging of CD8+ T cells in the malaria infected liver reveals key processes for effective protection

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CD8+ T cells can kill *Plasmodium* parasites in the liver of the mammalian host; a protective effect that can be harnessed for malaria vaccination. We have previously used intra-vital imaging to measure the interaction of CD8+ T cells in the liver and *Plasmodium* infected hepatocytes. We have previously observed that CD8+ T cells in the liver undertake LFA-1 dependent crawling motility in the allowing them to scan the liver and find infected hepatocytes. Subsequently we have observed that clusters of CD8+ T cells form around the infected hepatocyte, which may potentiate parasite killing. Key questions are how do these clusters form? And how are the parasites killed? Mathematical modelling suggested that clusters could form by at least two different processes. In the first process clusters form as a result of a positive feedback loop in which cells in the cluster recruit further effectors. Another model posits that clusters may form because it becomes harder for cells to leave the vicinity of an infected hepatocyte as clusters increase in size. To distinguish these possibilities we have imaged the behaviour of T cells in the liver to determine if they show evidence of directed migration towards infected hepatocytes. Moreover using Pertussis toxin mediated inhibition of chemokine receptors, chemokine receptor knockout mice and mice lacking key effector molecules we aim to understand the molecular processes underlying T cell clustering and parasite killing.

Mathematical and experimental approaches to understand immune response to infection / 393

Understanding age-specific differences in immune cell dynamics

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Age plays an important role on immunity across the lifespan, as both very young and very old individuals are at higher risk of severe infection. CD8 T cells are important for controlling a number of viral and bacterial infections, and both the number and phenotype of CD8 T cells change with age. Various mathematical and experimental methods have been used to analyse T cell kinetics,

and most of them assume a homogeneous population of cells. This assumption has been challenged experimentally and theoretically, that cells produced early in life may have different behaviour to those produced recently. We have recently developed a novel experimental model to 'timestamp' CD8 T cells in mice. More specifically, double positive CD8 T cells can be labeled in the thymus (using CD4 promoter tamoxifen-inducible cre to drive the expression of RFP permanently), thus the survival of these cells can be tracked over time.

Cells produced early in life show a faster decay, which then slows with time-since-production of the cell. Cells produced at later ages show a more stable behaviour, and their rate of decay also slows with time-since production of the cell. Comparing various mathematical models (based on the AIC values), we found that the population of T cell can be described by a model with three parameters. The model has an initial decay rate of cells made at birth, how the decay rate changes with the age of the host, and how the decay changes with the age of cell (since cell production).

Using the best-fit parameters from the model, we can develop another model about the 'layering' of cells made at different ages, and how this contributes to the total T cell pool. Based on our model, in a 300-day-old mouse, only 20% of the cells were made recently. We also modelled the process of cellular differentiation, and how this changes with age. The model can be described by a system of differential equations with non-constant parameters. We found that cells made early in life show a higher rate of differentiation.

Overall, this reveals an age-dependent heterogeneity in *in vivo* survival of CD8 T cells.

Mathematical and experimental approaches to understand immune response to infection / 350

A systems immunology approach to study immune responses against viral infection

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CD8+ T (CTL) cells play a pivotal role in protection from viral infection. Better understanding of the heterogeneous phenotypes of T cell subsets evolving during an immune response is timely needed for development of T cell based vaccines that can provide long-term immune protection. Viruses causing chronic infections such as HIV and HCV, trigger a T cell response characterised by functional exhaustion, and accumulation of immune escape variants. We have developed a single cell approach to identify and link functional phenotype, gene expression profile, TCR diversity and T cell avidity with the onset of exhaustion and its relationship with immune escape.

We analysed a cohort of prospectively followed subjects from acute primary HCV infections to disease outcome (clearance and chronicity). Antigen specific (Ag-) CTL were identified via epitope discovery and functional validation via IFN γ -ELISPOT. Index sorting was utilised to link surface phenotyping with gene expression profile. Full length TCR $\alpha\beta$ repertoire was identified from scRNAseq data using novel tools. Exhaustion was detected early on in the acute phase of infection and in CTL targeting conserved but also immune escape epitopes. Single cell RNAseq showed a distinct gene expression profile of exhausted T cells compared to the less differentiated subsets. In contrast, Ag-CTL in subjects that cleared HCV, polyfunctional (IFN γ , granzyme, and perforin) responses were found, with a highly diverse TCR repertoire. We discovered a novel T cell clone, characterised by high avidity for viral epitope, elevated IFN γ productions and polyfunctional phenotype.

This systems immunology approach provides new routes to investigate complex T cell dynamics and to identify new mechanisms to exploit in vaccine and immunotherapy.

Mathematical and experimental approaches to understand immune response to infection / 440

Evidence for independent fate competition within B lymphocytes: CD40 signal strength regulates the rate of B cell differentiation to plasmablasts by altering their time to divide only

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During the adaptive immune response, T and B lymphocytes receive and integrate signals from different sources that determine the strength and type of response they follow. Here we asked how reducing stimulation strength through the CD40 receptor could lead to an accelerated division-linked B cell differentiation, as noted in an earlier study [Hawkins *et al.*, Nat Comms 2014]. We observed using flow cytometry that reducing CD40 stimulation strength had two effects on B cell fates in vitro: it slowed down B cell division, and produced a greater proportion of differentiated plasmablasts in each subsequent generation. We studied this system with direct time-lapse imaging to observe division, death, and differentiation to Blimp-1+ plasmablasts, after 3-4 days in culture. We found that strength of stimulation by CD40 affected division times, as predicted, whereas times to die and times to differentiate to plasmablasts were unaffected. We could also show, by fitting mathematical models, that simple fate competition between division and differentiation could explain the accelerated differentiation by slowing division alone. Thus, our data suggest that weakly CD40 stimulated B cells divide slowly, and as a consequence, have more time to undergo differentiation before their next mitotic event. By understanding how different components of the B cell response are controlled and affected by regulatory signals, we aim to build up models of complex signal integration by cells that can predict net immune outcome. Successful models built in this way have many potential applications such as rational immunotherapy design.

Mathematical modelling of malaria: Dynamics within-host and between-hosts / 202

Analysis of high-frequency telemetry data using machine learning enables differentiation of stages of *Plasmodium knowlesi* infections in non-human primates

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High-frequency physiological data poses unique challenges for signal processing and computational analysis. This dataset was obtained from a cohort of *Macaca mulatta* and *Macaca fascicularis* infected with *Plasmodium knowlesi* using a customized telemetry system. The data set is comprised of electrocardiogram signals collected at a sampling rate of 1 kHz, temperature measures collected at 1 Hz, accelerometer data collected at 10 Hz, and blood pressure readings collected at 500 Hz. The implanted telemetry devices allowed nearly uninterrupted time series data acquisition over the course of an

infection experiment. Machine learning algorithms using daily features were used to accurately classify a day of telemetry data between pre-infection and liver stage over 90% of the time. The experimental design, analysis, and framework used to address challenges in multi-scale telemetry signal processing will be discussed.

Mathematical modelling of malaria: Dynamics within-host and between-hosts / 79

New mathematical models for artemisinin-induced parasite killing and growth retardation in blood-stage *Plasmodium falciparum*

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Falciparum malaria is a major parasitic disease causing widespread morbidity and mortality globally. Artemisinin derivatives – the most effective and widely-used antimalarials that have helped reduce the burden of malaria by 60% in some areas over the past decade – have recently been found to induce growth retardation of blood-stage *Plasmodium falciparum* when applied at clinically relevant concentrations. Furthermore, novel in vitro experiments indicate a complex relationship between drug concentration, the duration of exposure, and the rate of parasite killing.

In this presentation I will discuss how extensions to the pharmacokinetic-pharmacodynamic (PK-PD) modelling paradigm are required to explain in vitro observations and discuss the implications for our understanding of drug action. Given the stage sensitivity of the parasite to drug and the short half-life of the artemisinin derivatives in vivo, our model-based analyses suggest how drug resistance may manifest and how alternative dosing strategies, or alternative antimalarials with altered pharmacokinetic properties, may aid in maintaining clinical efficacy.

Mathematical modelling of malaria: Dynamics within-host and between-hosts / 139

Intermittent preventive treatment and the spread of drug resistant malaria parasites

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Over the last decade, control measures have significantly reduced malaria morbidity and mortality. However, the burden of malaria remains high, with more than 70% of malaria deaths occurring in children under the age of five. The spread of antimalarial resistant parasites challenges the efficacy of current interventions, such as Intermittent Preventive Treatment (IPT), whose aim it is to protect this vulnerable population. Under IPT, a curative dose of antimalarial drugs is administered along with a child's routine vaccinations, regardless of their infection status, as both a protective measure and to treat subclinical infections. We have developed mathematical models to study the relative

impact of IPT in promoting the spread of drug resistant malaria (compared with treatment of clinically ill individuals), and the combined effect of different drug half-lives, age-structure and local transmission intensity on the number of childhood deaths averted by using IPT in both the short and long-term in malaria endemic settings. I will also discuss some consequences of unstable and seasonal transmission of malaria on the efficacy of IPT.

Mathematical modelling of malaria: Dynamics within-host and between-hosts / 286

Optimal control and temperature variations of malaria transmission dynamics

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In this seminar, I will present the results obtained from investigating the optimal control strategies for malaria in the presence of temperature variation using a temperature dependent malaria model. A 2015 study by Augusto *et al.* identified the suitable temperature ranges for mosquitoes in four different geographical regions of Sub-Saharan Africa as [22.61°C - 28.58°C] in West African cities, [16.68°C - 27.92°C] in Central African cities, [19.04°C - 26.75°C] in East African cities, and [16.66°C - 25.32°C] in Southern Africa. The optimal control strategies in these temperature ranges suggest on average a high usage of both larviciding and adulticiding followed by a moderate usage of personal protection such as insecticide-treated bednet. The average optimal bednet usage mimics the trajectory of the mosquitoes as the mosquitoes respond to temperature variations. These results triggered the investigation of the impact of insecticide resistance mosquitoes on disease burden in the face of temperature variations. The results indicate that optimal bednet usage on average is higher in the presence of insecticide resistance mosquitoes. Furthermore, on average bednet usage increases as temperature increases to the optimal temperature suitable for mosquitoes and it decreases thereafter, a pattern similar to earlier results involving insecticide sensitive mosquitoes.

Mathematical models of cell motility and cancer progression in microenvironment: design, experiments, mathematical framework, and hypothesis test / 110

From crawlers to swimmers- mathematical and computational problems in cell motility

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Cell locomotion is essential for early development, angiogenesis, tissue regeneration, the immune response, and wound healing in multicellular organisms, and plays a very deleterious role in cancer metastasis in humans. Locomotion involves the detection and transduction of extracellular chemical and mechanical signals, integration of the signals into an intracellular signal, and the spatio-temporal control of the intracellular biochemical and mechanical responses that lead to force generation, morphological changes and directed movement. We will discuss some of the mathematical and computational challenges that the integration of these processes poses and describe recent progress on some component processes.

Mathematical models of cell motility and cancer progression in microenvironment: design, experiments, mathematical framework, and hypothesis test / 429

How the extracellular matrix promotes the growth of ovarian cancer

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Epithelial Ovarian Cancer (EOC) is one of the deadliest cancers in women. It is the fifth leading cause of cancer-related deaths in the United States. Due to the lack of early detection, this cancer has an average 5-year survival of only 27%. We know, that like other epithelial cancers, ovarian tumour cells remodel the extracellular matrix (ECM) components in healthy tissue in order to promote a favourable environment for replication and progression. However, the role of ECM in promoting EOC is yet to be explored. In this presentation, we aim to highlight some of the key ECM components that play a major role in the progression of tumour cells. We do this by considering the ECM as a dynamic system that can support and protect tumour cells by adapting its components. Using a system of networked ordinary differential equations, we model the tumour environment and show that, to understand the role of the ECM in tumour progression, we must consider the ECM as a collective entity and not just as individual components.

Mathematical models of cell motility and cancer progression in microenvironment: design, experiments, mathematical framework, and hypothesis test / 58

The metastatic reproduction number

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The mathematical modelling of metastasis is a challenge. The occurrence of metastasis is basically random, hence the use of stochastic modelling seems appropriate. We introduce a stochastic process called branched random walk with settlement to derive equations for the expected number of particles, the variance, the furthest particle and the extinction probability. We are able to identify a parameter R_0 , such that metastasis spread for $R_0 > 1$ and they die out for $R_0 < 1$. Hence we call R_0 the metastatic reproduction number. We compare this index to experimental outcomes in animal studies and we discuss its relevance for the treatment of metastasis.
Joint work with A. Rhodes and C. Frei.

Mathematical models of cell motility and cancer progression in microenvironment: design, experiments, mathematical framework, and hypothesis test / 86

Complex Role of NK cells in regulation of OV-Bortezomib therapy

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Oncolytic viruses such as herpes simplex virus-1 (oHSV) are genetically modified to target and kill cancer cells while not harming healthy normal cells and are currently under multiple clinical trials for safety and efficacy [1]. Bortezomib is a peptide-based proteasome inhibitor and is an FDA-approved drug for myeloma and mantle cell lymphoma. Yoo *et al.* [2] have previously demonstrated that bortezomib-induced unfolded protein response (UPR) in many tumour cell lines (glioma, ovarian, and head and neck) up-regulated expression of heat shock protein 90 (HSP90), which then enhanced viral replication through promotion of nuclear localization of the viral polymerase in vitro. This led to synergistic tumour cell killing in vitro, and a combination treatment of mice with oHSV and bortezomib showed improved anti-tumour efficacy *in vivo* [2]. This combination therapy also increased the surface expression levels of NK cell activating markers and enhanced pro-inflammatory cytokine secretion. These findings demonstrated that the synergistic interaction between oHSV and bortezomib, a clinically relevant proteasome inhibitor, augments the cancer cell killing and promotes overall therapeutic efficacy. Therefore, there is a sound ground for combining these agents in a clinical trial. In the present paper we investigated the role of NK cells in combination therapy with oncolytic virus (OV) and bortezomib. NK cells display rapid and potent immunity to metastasis and hematological cancers, and they overcome immunosuppressive effects of tumour microenvironment. We developed a mathematical model, a system of PDEs, in order to address the question of how the density of NK cells affects the growth of the tumour. We found that the anti-tumour efficacy increases when the endogenous NKs are depleted, and also when exogenous NK cells are injected into the tumour. These predictions were validated by our *in vivo* and *in vitro* experiments.

[1] Kanai R, Wakimoto H, Cheema T, Rabkin SD (2010) Oncolytic herpes simplex virus vectors and chemotherapy: are combinatorial strategies more effective for cancer? *Future Oncology* 6(4):619–634.

[2] Yoo J, *et al.* (2014) Bortezomib-induced unfolded protein response increases oncolytic hsv-1 replication resulting in synergistic antitumor effect, *Clin. Cancer Res.*, 20(14), 3787–3798.

Mathematical models of cell motility and cancer progression in microenvironment: design, experiments, mathematical framework, and hypothesis test / 124

Local and systemic consequences of radiation

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To date we have no understanding of why two patients with similar clinical stage and molecular profile would have different radiotherapy outcomes. Reliable biomarkers are direly needed to predict which patients will be cured, with the hope to de-escalate dose when possible or increase where necessary. It is increasingly appreciated that radiation can induce a robust antitumour immune response that provides a second wave of cell kill and tumour regression. We develop a variety of mathematical models to study the local and systemic cytotoxic and immunological consequences of radiation therapy and discuss their clinical implications.

Mathematical strategies to overcome resistance to anticancer drugs / 506

Control structures in cancer chemotherapy

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Drug resistance is a major cause of the failure of chemotherapy. Resistance manifests through a diverse set of molecular mechanisms, such as the upregulation of efflux transporters on the cell membrane, enhanced DNA damage repair mechanisms, and/or the presence of cancer stem cells. Classically, these mechanisms are understood as conferred to the cell by random genetic mutations, from which clonal expansion occurs via Darwinian evolution. However, the recent experimental discovery of epigenetics and phenotype plasticity complicates this hypothesis. It is now believed that chemotherapy can produce drug-resistant clones. Motivated by this recent experimental evidence, we introduce a framework of drug-induced resistance, which incorporates both random and drug induced effects. We discuss both structural and practical identifiability issues related to the model, and demonstrate techniques by which the induction rate of an applied chemotherapy may be experimentally determined. This is crucial, as the design of control protocols is heavily influenced by this aforementioned rate. Specifically, we seek the treatment protocol which prolongs patient's life by maximizing the time of treatment until a critical tumour size is reached. The general control structure is determined as a combination of both bang-bang and singular arcs. We deduce that in the case of purely random mutations, optimal controls are pure bang-bang, while singular arcs exist if treatment causes resistance to emerge. We further characterize the precise control structure using a combination of numerical methods and higher-order techniques. Thus, the ability of a drug to induce resistance generates a completely different control structure from that of the classical Darwinian selection paradigm.

Mathematical strategies to overcome resistance to anticancer drugs / 376

Modelling continuous levels of resistance to multidrug therapy in cancer

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Multidrug resistance consists of a series of genetic and epigenetic alternations that involve multifactorial and complex processes, which are a challenge to successful cancer treatments. Accompanied by advances in biotechnology and high dimensional data analysis techniques that are bringing in new opportunities in modelling biological systems with continuous phenotypic structured models, we study a cancer cell population model that considers a multi-dimensional continuous resistance trait to multiple drugs to investigate multidrug resistance. We compare our continuous resistance trait model with classical models that assume a discrete resistance state and classify the cases when the continuum and discrete models yield different dynamical patterns in the emerging heterogeneity in response to drugs. We also compute the maximal fitness resistance trait for various continuum models and study the effect of epimutations. Finally, we demonstrate how our approach can be used to study tumour growth regarding the turnover rate and the proliferating fraction, and show that a continuous resistance level may result in a different dynamics when compared with the predictions of other discrete models.

Mathematical strategies to overcome resistance to anticancer drugs / 483

Mathematical models on tumour-lymphocyte dynamics and checkpoint blockade therapy

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Cytotoxic T-lymphocytes, commonly called killer T cells, are among our immune system's most potent and well-understood weapons against cancer. However, checkpoint receptors such as CTLA-4 and PD-1 on the surfaces of T cells inhibit their activation and proliferation. These receptors can be blocked by antibody drugs, which pave the way for an anti-tumour immune response. We will present work-in-progress mathematical models on tumour-lymphocyte dynamics in the presence of checkpoint blockade therapy, discuss their clinical implications, and more broadly discuss the current modelling efforts in this area.

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Agent-based modelling demonstrates the impact of localised tumour cell proliferation and death on macrophage infiltration

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Growing tumours are infiltrated by a variety of immune cells, including macrophages, a type of immune cell which can adopt a range of pro- or anti-tumour phenotypes depending on microenvironmental cues. The spatial distribution of macrophages within a tumour varies from patient to patient and between different tumour types, and is related to patient outcome. There is considerable interest in understanding the mechanisms regulating the spatial localisation of macrophages within solid tumours and in exploiting tumour associated macrophages to deliver treatment to cancer cells [1, 4].

As a first step to understanding patterns of macrophage localisation within solid tumours, we consider the roles played by tumour cell proliferation and death in driving cell movement from proliferative tumour regions to hypoxic regions. This movement, induced by oxygen gradients within a tumour, must be taken into consideration when characterising patterns of macrophage infiltration. To understand the impact that this background movement has on macrophage infiltration, we first consider the infiltration of inert polystyrene microbeads into a tumour spheroid using data from [2]. We use the CHASTE modelling framework [3] to develop an agent-based model of microbead infiltration into a spheroid, and show how varying the rates of tumour cell proliferation and death influences the patterns of bead infiltration into the tumours.

We then extend our model to include macrophages and CSF-1, a macrophage chemoattractant produced by hypoxic tumour cells. By comparing the infiltration patterns of the macrophages in this model with those of the microbeads, we identify components of macrophage infiltration due to active (chemotactic) movement and passive components associated with tumour cell proliferation and death. Identifying which variations in macrophage distribution are due to active or passive processes may help determine which patients are most likely to respond to treatment with CSF-1 inhibitors [4].

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- [2] Dorie, M. J., Kallman, R. F., Rapacchietta, D. F., Van Antwerp, D., & Huang, Y. R. (1982). Migration and internalization of cells and polystyrene microspheres in tumor cell spheroids. *Experimental Cell Research*, 141(1), 201–209. [http://doi.org/10.1016/0014-4827\(82\)90082-9](http://doi.org/10.1016/0014-4827(82)90082-9)
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Mathematics neuroscience subgroup / 391

Spatio-temporal canards & bifurcation delay in neural reaction-diffusion systems

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Neural spiking and bursting rhythms in space-clamped (i.e., ODE) models are typically driven by either canard dynamics or slow passage through Hopf bifurcations. In both cases, solutions which are attracted to quasi-stationary states (QSS) sufficiently before a fold or Hopf bifurcation remain near the QSS for long times after the states have become repelling, resulting in a significant delay in the loss of stability and hence in the onset of oscillations. In this work, we present the spatio-temporal analogues of these delayed bifurcation phenomena in multi-time-scale reaction-diffusion equations. We show the existence of canard-induced bursting rhythms in a spatially extended model of the electrical activity in pituitary cells. We then derive asymptotic formulas for the space-time boundaries that act as buffers beyond which solutions cannot remain near the repelling QSS (and hence at which the delayed onset of oscillations must occur) for slow passage through Hopf bifurcations in reaction-diffusion equations.

This is joint work with Tasso J. Kaper (Boston University).

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Low- and high-waking modes in the corticothalamic system

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In this talk presented at the Mathematical Neuroscience Subgroup Minisymposium I will discuss a numerical analysis of the steady-state solutions of a neural field model of the corticothalamic system. The independent synaptic connections of the corticothalamic model define an eight-dimensional parameter space, while specific combinations of these connections parameterize intracortical, corticothalamic, and intrathalamic loops.

The first part of the analysis consists of a systematic identification of multistable regions for physiological parameter ranges representing normal arousal waking states in adult humans. Parameter values have been derived from human electroencephalographic recordings (EEG). The key results

are the confirmation of the existence of up to five steady-state solutions, up to three of which are linearly stable. The presence of multiple stable steady-state solutions implies that the system has enough degrees of freedom to capture multiple operating points (e.g., multiple global brain states). Indeed, two out of the three linearly stable steady-state equilibria represent two waking modes for adult human physiology while resting with the eyes closed. These two modes are termed the low- and high- waking modes.

While the low-waking mode has been previously identified with normal brain activity during quiet wakefulness, the high-waking mode has not been fully characterized. The second part of the analysis focus on (i) the spectral features of high-waking mode states; (ii) the nonlinear attractors between the two waking modes; and, (iii) the switching dynamics between the low- and high-waking modes using small amplitude and bandlimited random perturbations.

We argue that the high-waking mode may represent hyperarousal waking states. This result opens up the possibility to predict and identify subtypes of primary insomnia in which cortical hyperarousal is the main hallmark from human neuroimaging data.

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Volume transmission and neurotransmitter homeostasis

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In volume transmission, neurons in one brain nucleus send their axons to a second nucleus where neurotransmitter is released into the extracellular space. In [1] we showed how to calculate the average amount of neurotransmitter at different parts of the extracellular space, depending on neural properties and the geometry of the projections and extracellular space. We showed how to formulate questions as boundary value problems for the heat equation with stochastically switching boundary conditions, and we derived results in one space dimension.

Here we discuss the two- and three-dimensional problems, along with mechanistic models of neurotransmitter homeostasis.

[1] Lawley, Best, Reed 2016

Mathematics neuroscience subgroup / 438

Temperature sensitivity of PO/AH neurons

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Thermoregulatory responses are partially controlled by the preoptic area and anterior hypothalamus (PO/AH), which contains a mixed population of temperature-sensitive and insensitive neurons. In [1] based on physiological data, a Hodgkin-Huxley-like conductance based model was constructed. This model suggests that most PO/AH neurons have the same types of ionic channels, but different

levels of channel expression can explain the inherent properties of the various types of temperature-sensitive and insensitive neurons which is encoded in their frequency sensitivity relative to temperature.

Here we present a detailed bifurcation analysis of this model to confirm these observations. We focus on three main physiological bifurcation parameters, the temperature T and the maximum conductances of two specific background potassium leak channels, g_{task} and g_{trek} , that are known to be expressed in these PO/AH neurons. These three bifurcation parameters are sufficient to explain the dynamics of PO/AH neurons observed in experiments.

If time permits, we also discuss the multiple timescales inherent in this model and explain the creation of action potentials based on a geometric singular perturbation analysis.

[1] Wechselberger *et al.*, 2006

Modelling feedback-mediated flow dynamics / 209

Development and validation of a model of renal oxygen transport in the rat renal medulla

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Background and Purpose: Renal hypoxia is postulated to be a leading cause of acute kidney injury, and the renal medulla is known to be most susceptible to hypoxia. The ability to accurately predict normal and abnormal oxygen states in terms of tissue oxygen tension (PO₂) within the renal medulla is highly desirable, as among other uses predicted medullary PO₂ can be correlated with local tissue damage. In this study, we have developed a computational model for blood and oxygen transport within the renal medulla to estimate medullary tissue PO₂.

Materials and Methods: A multiscale modelling approach was used to model the blood flow and oxygen transport within a realistic 3-D medullary geometry. At the macroscale level, the blood flow in the medullary vasa recta was modelled using a set of three, coupled, 3D porous media models, each representing the blood flow in the descending vasa recta, long ascending vasa recta, and short ascending vasa recta. Another set of three advection-diffusion models, each coupled with a blood flow model, were employed to simultaneously represent the oxygen transport throughout the whole medulla. In addition to the six top-level models, four diffusive oxygen transport models were employed at the microscale level to describe the distribution of oxygen in two spatial dimensions across the renal tissue surrounding the vasculature. Each low-level model represents a single vascular bundle and associated tissue. The low-level models were located in the outer and inner stripes, near the base and near the tip of the inner medulla. The model predictions, based on reported geometry, model parameters, boundary conditions and source-sink terms obtained from the literature on the rat kidney were found by iterating between the macroscale and microscale sub-models until all ten sub-models were satisfied simultaneously.

Results & Discussion: The model predictions were validated by simulating eight sets of published experimental data in rats (four sets of control groups and four sets of treatment groups, reported in four independent papers). These experiments examined the effects of acute hemodilution, acute renal ischemia/reperfusion (IR), and chronic administration (30 days) of dinitrophenol (DNP). For each validation test, model parameters were altered according to experimental observations. Tissue and/or microvascular PO₂ predicted by the model was then compared with that observed experimentally.

All model predictions for control groups were within ± 1 standard error of the mean (SEM) value observed experimentally. Most of the model predictions for treatment groups were also within \pm

1 SEM, except for later stages in the acute hemodilution experiment, where the model predicted PO₂ exceeded the measured PO₂ by more than 7 SEM. Deviations from the model predictions are probably due to unidentified external or intra-renal processes, triggered by pathologic processes, but not accounted for in the model or measured in the experiments.

Conclusion: The validation tests confirmed that the proposed renal medullary PO₂ model is robust and can accurately capture the behaviour of renal medullary oxygenation in both normal and early pathologic states in the rat.

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Predicting blood flow and oxygenation in an image-based retinal vascular network

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Impaired oxygen delivery and blood flow have been identified as significant factors that contribute to the loss of retinal ganglion cells in glaucoma patients. It is unknown, however, whether changes in blood flow to the retina are the cause or effect of retinal ganglion cell death, and a combined experimental and theoretical approach is needed to analyze the relationship between blood flow impairment and glaucoma. In this talk, recent data-driven theoretical models will be presented that predict how issues with blood flow regulation could lead to the impaired oxygenation seen in experimental glaucoma data. Then, an updated representation of the retinal vasculature based on confocal microscopy images will be introduced. These images reveal a complex and heterogeneous geometry of vessels that are distributed non-uniformly into multiple distinct retinal layers at varying depths. As a result, an updated model using a Green's function method is used to predict oxygen saturation in the retinal arteriolar tree, in addition to predicting blood flow in the entire vascular network. Finally, a framework will be introduced to incorporate time-dependent blood flow regulation into the model, so that vessels in the network can adjust diameters in response to changing conditions. The predictions from this mathematical model will be used to address the controversy of the cause-and-effect relationship between retinal ganglion cell death and impaired blood flow in glaucoma.

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Synchronization of tubular pressure oscillations in coupled nephrons

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The kidney plays an essential role in regulating the blood pressure and a number of its functions operate at the functional unit of the kidney, the nephron. To understand the impacts of interneuron coupling on the overall nephrons' dynamics, we develop a mathematical model of a tubuloglomerular feedback (TGF) system, a negative feedback mechanism for nephron's fluid capacity. Specifically, each model nephron represents a rigid thick ascending limb only and is assumed to interact with nearby nephrons through vascular and hemodynamic coupling along the pre-glomerular vasculature. We conduct a bifurcation analysis by deriving a characteristic equation obtained via a linearization

of the model equations. Numerical solutions for the model equations are consequently obtained to validate the predictions of the characteristic equation. The model results show that the coupled-TGF system with two different coupling effects can produce in-phase as well as anti-phase (out-of-phase) synchronization of tubular pressure oscillations in two coupled nephrons, as has been observed in experimental studies.

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The relationship between blood flow, oxygen consumption and blood oxygen levels during transient local activation of the cerebral cortex

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Transient activation of a region of the brain cortex results in an increase in the local rate of oxygen consumption, and stimulates an increase in blood flow to the stimulated region, a phenomenon known as neurovascular coupling. Under normal conditions, the relative increase in blood flow during activation is observed to exceed the relative increase in oxygen consumption, by a factor $n > 1$. As a consequence, the oxygen content of blood in the stimulated region increases. The associated change in hemoglobin saturation forms the basis for the blood oxygen level dependent (BOLD) signal detected during functional magnetic resonance imaging (fMRI) of the brain. Despite the extensive use of this technique, its physiological basis is incompletely understood. While MRI techniques allow simultaneous observations of local cerebral blood flow (CBF) and the BOLD signal, oxygen consumption rate cannot be measured with similar spatial and temporal resolution. Here, a Krogh-cylinder-type theoretical model was used to analyze the relationship between blood flow, oxygen consumption and hemoglobin saturation during transient activation of rat somatosensory cortex. The equations for time-dependent convection and diffusion of oxygen in the blood and tissue were solved using the finite-element method. Experimental data [1] on variation in blood flow and hemoglobin saturation were used to deduce parameters describing the time-dependent variation in oxygen consumption rate. The value of n was found to be approximately 3, consistent with observations in other experimental models. Experimental BOLD signals show a brief initial dip in hemoglobin saturation at the start of activation, although this is not consistently observed. In the simulations, such an initial dip was predicted and shown to be sensitive to the timing of the increase in flow relative to the increase in consumption. This theoretical model provides a method for deducing time-varying oxygen consumption rate from BOLD fMRI observations of the locally stimulated cerebral cortex. Such data can be used to investigate the dynamical characteristics of neurovascular coupling.

[1] Masamoto *et al.*, *NeuroImage* 40:442, 2008

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Modelling gene drives / 270

Gene drive localization and reversal

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Gene drives are a powerful technique to reduce the size of a population or to transform it to become less troublesome. Major concerns include accidental escape of a gene drive, which might lead to widespread elimination of a species, or unintended consequences of released individuals, which might include evolution of resistance to an effector gene. Both spatial localization of a gene drive and the ability to reverse a gene drive are desirable mechanisms to increase the safety of drives. A number of such approaches have been proposed in the literature. Using mathematical modelling, we will explore their likely efficacy and discuss critical weaknesses.

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MGDrive: a simulation framework for gene drive in spatially-explicit mosquito populations and its application to threshold-dependent systems

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The advent of CRISPR/Cas9-based gene editing and its demonstrated ability to streamline the development of gene drive systems has reignited interest in its application to the control of mosquitoes and the diseases they transmit. The versatility of this technology has also enabled a wide range of gene drive architectures to be realized, creating a need for their population-level and spatial dynamics to be explored. To this end, we present MGDrive (Mosquito Gene Drive Explorer): a simulation framework designed to investigate the population dynamics of a variety of gene drive architectures and their spread through spatially-explicit mosquito populations. MGDrive is based on a tensor algebraic generalization of the lumped age-class model of mosquito ecology. Treating these population dynamic equations in a variable-dimension tensor form allows them to be left unchanged while modifying the dimensionality of the tensor describing inheritance patterns, as required by the drive system. Spatial dynamics are accommodated through a metapopulation structure in which lumped age-class models run in parallel and migrants are exchanged between metapopulations at defined rates. Example MGDrive simulations are presented for threshold-dependent drive systems: a) reciprocal chromosomal translocations, and b) toxin-antidote-based underdominant systems. Criteria are described for which these systems may be confined to their release community without spreading to neighboring communities.

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The spatial dynamics of selfish genetic elements in *Aedes aegypti* arbovirus vector populations

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Novel strategies for controlling mosquito vectors of human diseases involve introductions of selfish genetic elements (SGEs), or elements that spread through the mosquito population by means of non-Mendelian inheritance. The releases of the endosymbiotic bacteria *Wolbachia* into *Aedes aegypti* populations in order to reduce their capacity for arbovirus transmission are the first application of an SGE introduction strategy in a field setting. Gene drive technologies for creating SGEs

that reduce vectorial capacity are also being developed. SGEs are vertically transmitted between mosquito hosts, and their spread dynamics have complex interactions with natural mosquito population dynamics, population structure and fitness components. We develop a model of an *Ae. aegypti* metapopulation that incorporates empirical relationships linking variation in mosquito abundance to density-dependent fitness components. We first show that our model can produce patterns of demographic variation similar to those found in natural populations, and predict rates of spatial spread of *Wolbachia* matching those observed following field releases. We then explore different SGE release strategies over an operationally relevant spatial scale, and compare the spread dynamics of *Wolbachia* and gene drive. We find that the spatial release distribution strongly affects the rate of spread of both SGEs, with widely dispersed release distributions out-performing spatially aggregated distributions, especially when the SGE incurs fitness costs. Our results demonstrate how spatial and demographic structure in the mosquito host population impacts SGE spread, with implications for the design of effective release strategies.

Modelling gene drives / 310

Mathematical modelling of CRISPR gene drives for exotic vertebrate pest eradication

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Synthetically-constructed gene drives, that use CRISPR-Cas9 technology to bias inheritance of a particular gene, have been proposed for exotic pest eradication. This is a controversial idea, as there is an apparent potential risk in the use of such technologies, for example to non-target populations of the species. Further, the basic question – Is the technology actually able to achieve its goal in practice? – is vexed. I will discuss some of our work which has developed stochastic, individual-based models of a number of gene drive strategies that have been proposed for the possible eradication of exotic vertebrate pests. I will discuss some of the issues surrounding their likely effectiveness for eradication, explore the potential risks to non-target populations, along with considering options for alleviating these issues.

Modelling immune interactions with disease / 88

The role of Natural Killer cells in the development of a primary tumour mass and metastasis formation

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In recent years, advances in cancer research have shown that the body's immune response to tumour cells plays a significant role in fighting cancer growth. Although the immune system is intrinsically capable of destroying tumour cells, tumours and their microenvironment have an ability to suppress the immune response. Whereas the roles of some immune cells have been greatly studied, the role of Natural Killer (NK) cells is less clear. Despite the fact that studies have shown that NK cells are not very effective at penetrating the tumour environment and play a minimal role in the direct killing of tumour cells in a tumour mass, studies with NK cell immunotherapies in humans have shown great success. The leading cause of death for cancer is not primary tumour growth, but instead metastasis formation. In mice, depleting NK cells has shown to prevent metastasis formation. In order to understand the complex interplay between the primary tumour, the metastases, and the immune system, it is necessary to develop a model of tumour growth that includes these

immune subpopulations and their interactions with the tumour and with each other. Here, such a model is presented, consisting of 17 coupled ordinary differential equations and one stochastic ODE that capture the complex interplay between CD4+ and CD8+ T cells, regulatory T cells, NK cells, dendritic cells, MDSCs, and both immunostimulatory (IL-2, IFN-gamma) and immunosuppressive (IL-10, TGF-beta) cytokines or factors, the primary tumour, circulating tumour cells, and tumour metastases. All parameters are estimated from experimental data. The model shows that one of the main immune components contributing to the prevention of metastasis formation is killing of circulating tumour cells by NK cells. For tumours with high antigen expression on their surface, T cells play the primary role in preventing metastasis formation, however circulating tumour cells with low antigen expression are eradicated mostly by NK cells. With this model, it is possible to replicate experimental data of metastasis formation under NK cell depletion. Implications for considering immunologic effects of standard chemotherapy combinations, in particular FOLFOX for colorectal cancer, are discussed.

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Dynamical conditions for the containment of HIV infection by CD8+ T Cells – a variable structure control approach

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In the study of the Human Immunodeficiency Virus (HIV) infection dynamics, the reproductive ratio is a well known tool which provides a steady-state condition to determine the outcome of the infection. This paper assesses the control of HIV by the immune response. Dynamical conditions for the containment of HIV infection by the HIV-specific CD8+ T cell response are evaluated using a model of HIV dynamics in vivo in which HIV-infected cells are killed before they start producing new virion. The reachability paradigm from Variable Structure Control (VSC) theory is used to formulate a dynamical condition for immunity. Simulation results show that this reachability condition effectively monitors the immunological requirements to contain HIV. This work also suggests that the cytolytic killing mechanism of CD8+ T cells operates as a boundary layer control to contain HIV infection. Together, the findings indicate that in contrast to the reproductive ratio, the proposed VSC approach delivers a framework to assess the effects of nonlinear dynamics and uncertainty as well as providing a means to investigate immunotherapy strategies.

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Understanding the dynamics of reactivation from latency in macaques infected with tagged simian immunodeficiency virus

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Modern anti-retroviral therapy can effectively control HIV. However, the virus cannot be eradicated due to the presence of latently infected CD4+ cells that cause the reactivation of virus when a patient stops anti-retroviral treatment.

There is a lack of knowledge about the basic dynamics of reactivation of latently infected cells and the interaction of virus with immunity. We combined mathematical modelling with a novel experimental method of 'barcoded' viruses to quantify the contribution of individual latently infected cells.

Rhesus macaques were infected intravenously with a sequence-tagged SIV-M virus with ~10,000 different barcodes. Animals were treated with antiretroviral therapy for various times prior to treatment interruption. After interruption serum samples were subjected to gene sequencing in order to identify the frequency of individual barcoded viruses.

We developed a mathematical model of growth of virus from different latently infected cells. Applying this model to experimental data we estimate that the frequency of reactivation from latency ranges from around 20 reactivations per day to 0.5 reactivations per day, depending on the timing and duration of treatment. A single reactivated latent cell can produce an average viral load equivalent to ~0.1-0.5 viral copies/ml of virus, depending on assumptions about duration of drug action.

We have also studied the virological parameters that may predict reactivation rate. When comparing animals treated starting on day 4 and day 27 post-infection and find that monkeys treated on day 4 have 40-fold higher reactivation rate per SIV DNA copy than monkeys treated on day 27. This difference cannot be simply explained by differences in immune activation or immune response. We analyse this by modelling the dynamics of DNA accumulation and viral-immune interactions.

The combination of mathematical modelling of viral dynamics of barcoded virus provides a powerful tool to understand latency formation, maintenance and reactivation in SIV / HIV.

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Cell adhesion and dynamic fibre redistribution within two-scale moving boundary cancer invasion

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Cancer cell invasion, recognised as one of the hallmarks of cancer, is a complex process involving the secretion of matrix-degrading enzymes that have the ability to degrade the surrounding extracellular matrix (ECM). Combined with cell proliferation, migration, and changes in cell-cell and cell-matrix adhesion, a tumour is able to spread into the surrounding tissue. We highlight the multiscale character of this process through a double feedback link between the cell-scale molecular processes and those occurring at the tissue level. In order to gain a deeper understanding of the mechanics of cancer cell invasion, we look to further investigate the surrounding microenvironment of a tumour.

The ECM is a key biological structure that not only provides structure and support to surrounding cells, but also acts as a platform on which the cells can communicate and exercise spatial movement. There are several other vital structures within the ECM, however we are going to focus primarily on fibrous proteins, such as fibronectin. These fibres are key players in the function of healthy cells, contributing to many essential processes such as cell migration, differentiation, migration and proliferation. They also play a crucial role in tumour progression with the ability to anchor cells to other components of the ECM.

In this work we consider the two-scale dynamic cross-talk between cancer cells and a two component ECM (consisting of both a fibrous and a non-fibrous phase). To that end, we incorporate the dynamics interlinked macro-micro cells-ECM interactions within inside the tumour support that contributes simultaneously both to cell-adhesion and to the dynamic re-arrangement and restructuring of the ECM fibres. Furthermore, this is embedded within a multiscale moving boundary approach

for the cancer cell population in the presence of cell-adhesion at the tissue scale and matrix degrading enzyme molecular processes and fibre redistribution considered at cell-scale. Computational simulations will accompany the presentation of the overall modelling framework to examine the impact of different levels of adhesion between cells in conjunction with the continuous ECM fibres restructuring on cancer invasion patterns.

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Dynamics of HIV-1 coinfection under different susceptible target cell populations during cell-free infection in cell culture

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Human Immunodeficiency Virus typeI (HIV-1) mutations are rapidly accumulated through recombination events which are largely caused by HIV-1 coinfection [1]. Therefore, HIV-1 coinfection has the potential to produce the drug-resistant viruses, which leads to the high pathologies and disease progression. Recently, it has been reported that coinfection occurs more frequently than at random both *in vitro* and *in vivo* [1,2], implying that this viral phenomenon is quite common in HIV-1 infection. Furthermore, one possible mechanism of HIV-1 coinfection is driven by the different susceptibility of target cells [2,3]. Thus, the elucidation of HIV-1 coinfection associated with different susceptible target cell populations is required to more accurately capture the general viral mechanism in HIV-1 infection. In this study, we constructed ordinary differential equations considering the heterogeneity of target cell populations during cell-free infection in cell culture, and reproduced the cell culture experiment data. Interestingly, our mathematical analyses demonstrated that 2 different susceptible target cell subpopulations could explain coinfection experiments in cell culture using the AIC model selection. In addition, our novel finding is that coinfecting cells are emerged from the most susceptible subpopulation at 98.2% on average. Taken together, our mathematical-experimental approach suggested that the most susceptible target cell population is the dominant resource of HIV-1 infection in cell-free infection.

[1] Q. Dang *et al.*, 2004

[2] J. Chen *et al.*, 2005

[3] A. Remion, *et al.*, 2016

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Tumour-immune cells interaction shapes tumour morphology: evolutionary process drives mutations for emerging hallmarks

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The idea of cancer as an evolutionary disease is well established. Cancer development is driven by mutation and selective forces, including the action of the immune system, interspecific competition and therapies. Different tumour types exhibit resistance to the immune system suggesting the investigation of different aspects of the tumoural microenvironment to better understand cancer.

The tumoural tissue is composed of different phenotypes, occurred from genetic and epigenetic mutations and fixed by Darwinian selection. Evolutionary niches, set up by the competition-coexistence of different cancer clones and by the action of the immune system, can shape tumour form. An analysis of the tumoural morphology can help to classify cancer types, suggesting a ways to increase the effectiveness of the medical treatments.

The aim of this talk is to present a hybrid mathematical model comprising of an agent based model for the tumour-immune interaction and a system of delay differential equations for the T-cell activation cycle. Different tumour microenvironments are shown to influence the morphological evolution of the tumoural tissue and the genetic instability leading to crucial mutations. Shapes are correlated to different evolutionary outcomes that can be altered by therapies. Further, different treatments induce modifications to the environment and then to the final outcomes. In particular, immunotherapy cycles and molecular target therapy are studied. Finally, a statistical analysis of the model is used to discuss the reliability and the reproducibility of the outcomes.

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Mathematical modelling of immune dynamics in disease and treatment

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Immune system dynamics in the context of a number of diseases, including certain cancers and type I diabetes, continues to play an increasingly central role in the development of new treatment strategies. The critical importance of the immune system in fighting such diseases has been verified clinically, as well as through mathematical models.

Many open questions remain, however, including what may lead to non-uniform patient responses to treatments, and how to optimize and personalize therapy protocols. Mathematical models can help to provide insights into the mechanisms that may be influencing patient outcomes, and provide a way to investigate questions that are difficult, if not impossible, to address in any other way. In this talk, we will present a sampling of mathematical models we have developed that help us to simulate immune system interactions, disease dynamics, and treatment approaches that may slow, or even stop, disease progression.

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Host control of malaria infection is rarely mediated by host clearance

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Infections with the malaria parasite can lead to severe illness and mortality, with nearly half a million deaths attributed to malaria globally each year. Adults from malaria endemic regions often have immunity to malaria and are much less susceptible to disease, compared with children. Understanding how a host can control malaria infections is critical in guiding the development of a much needed efficacious vaccine. Infected individuals are thought to clear infected red blood cells (RBCs) from circulation via organs such as the spleen - and this clearance is thought to play a major role in controlling malaria infections. However, no work has directly quantified clearance of infected RBCs or studied the extent to which parasite clearance is improved in, for example, immune hosts.

In this study, we developed a unique experimental approach to directly track the loss of a single cohort of infected RBCs in mice. We used this system to study the loss of infected RBCs in naïve, immune deficient, acutely infected, drug treated and immune mice. Modelling data from these experiments enabled us determine the baseline clearance half-life of infected RBCs in naïve mice (14.4 h), which suggests that about one third of infected cells are cleared every parasite replication cycle. Further, we found that this half-life was approximately doubled when phagocytes (a certain host immune cell) were depleted (33.8 h), suggesting host immune cells are important in removing infected cells. Surprisingly, with the exception of treatment with a high dose of a particular antimalarial (sodium artesunate), we did not observe an increase in the rate of clearance of infected RBCs in acutely infected mice, immune mice, or after drug treated, despite observing effective control of infection in all scenarios. Instead, of elevated host removal of infected, we observed an array of other factors that caused the control of infection, and in particular, this work revealed a novel mechanism of host control in acute infection, that is, slowing the development of parasites.

This work has revealed that the basal rate of removal of infected RBCs in murine malaria infection is very high, but this rate cannot easily be improved by host responses or drug treatment.

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Mathematical modelling of potential mechanism for the restoration of the T-cell homeostasis along with a sustained decay in viral reservoir upon infusion of CCR5 gene edited T cells in HIV infected subjects

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Although antiretroviral therapy (ART) suppresses viral replication, patients still suffer from both low CD4 T-cell counts and HIV persistence, requiring them to remain on complex ART regimens for life. A naturally occurring 32-base pair deletion in the CCR5 gene, the major co-receptor for HIV entry, is associated with infection resistance.

In the study initiated by Sangamo Therapeutics, HIV-infected subjects received a single infusion of autologous CCR5-modified CD4 T-cells. Following infusion, we observed a sustained increase in the CD4 T-cells count (mean ~162 cells/ μ L) with a significant decrease in the HIV reservoir (median ~1 log 3yrs post infusion). Long-term persistence of CCR5-modified cells suggested their presence

within long-lived CD4 populations, such as T memory stem cells (TSCM). To investigate the impact of persistence of “HIV-resistant” TSCM on immune homeostasis and the decay of the HIV reservoir, we developed a mathematical model of T-cell dynamics. The model follows a linear transition from the naïve to effector memory (TEM) state and includes thymic input of naïve cells, proliferation, death and differentiation rates for naïve and memory cells. Model fits to patient data pre- and post-injection and sensitivity analysis results that increased thymic output, an increased TSCM proliferation rate, a decreased central memory cell death rate, and an increased central memory transition rate played an important role in increasing the T-cell count and decreasing the HIV reservoir.

Finally, using a bi-phasic decay model, we show that purging and replacement dynamics of the CD4 T-cells population post infusion account for a significant fraction of the observed decrease in the HIV reservoir. Our results indicate that homeostatic processes can control HIV persistence, and that T-cell restoration post infusion of CCR5-deleted cells leads to the decay of the HIV reservoir.

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Liver spatial heterogeneities and HBV

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The liver is a spatially complex and heterogeneous network of blood and bile flows coupled with metabolic processing and a favoured target for infection by hepatic viruses. We present here a mathematical model aimed at investigating these intrinsic heterogeneities and their impact on the dynamic of the Hepatitis-B variant (HBV). Dramatic spatio-temporal scaling from individual hepatocytes to the entire liver organ invites multi-scale approaches inspiring assembly of sinusoid-level ‘unit models’ into a whole organ representation. Each ‘unit-model’ sinusoid combines individual hepatocytes communicating with blood flow in the sinus in turn connected with other ‘unit-model’ sinusoids aggregated into a whole liver modelling scheme. This permits investigating impacts on the whole organ of precisely distributed spatial heterogeneities such as varying HBV uptake mechanisms (e.g., the sodium-taurocholate cotransporter or NTCP), immune cell responses (e.g., cytolytic or interferon-based) and simple efficiency of HBV replication. We present our results showing how heterogeneities of, in particular, HBV replication efficiencies may be responsible for persistent chronic infections.

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Memory and time delays in physiological regulation

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Memory translates into time delays naturally in a number of regulatory processes at all levels of organisation in the life sciences: transcription and translation times in molecular biology, finite axonal conduction velocities between neurons, maturation times of precursor cells in hematopoiesis and infection and temporary immune periods in infectious disease propagation are but a few examples of naturally occurring such delays. In many instances, mathematical constructions are elaborated to

avoid incorporating time delayed arguments in the modelling equations of the system of interest. We present, by way of examples on two specific physiological and epidemiological systems, the limitations of this approach and the extent to which these approximations may or may not be useful or necessary for a proper understanding of the modelled system.

This talk will serve as an introduction to the other presentations of the Minisymposium.

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Models for thrombopoiesis with bifurcation analysis

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Thrombopoiesis is the process for producing platelets, which uses a negative feedback to maintain homeostasis in normal individuals. However, pathological states exist where platelet concentrations in the body oscillate. An age-structured model for thrombopoiesis was developed and fitted to clinical data for subjects with normal and pathological platelet production. Variations on this model are described to obtain more details on how this system undergoes a Hopf bifurcation. Our study explores parameter sensitivity and which model features are most significant in the bifurcation to periodic solutions. We observed that near the Hopf bifurcation there is a very rapid transition of the stationary solution along with the change in the real part of the leading pair of eigenvalues. The creation and analysis of the characteristic equations from these models provide some interesting new ideas. Certain model reductions decrease the complexity of the characteristic equation and allow a better understanding of the source of the Hopf bifurcation. Our modelling efforts might improve insight into the primary problems underlying the diseased state, where levels of platelets and thrombopoietin vary periodically.

Modelling of dynamic cellular and sub-cellular systems / 192

Parameter estimation for modelling intermittent androgen suppression therapy in prostate cancer patients

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Advanced prostate cancer is often treated by androgen suppression therapy, since prostate cells depend on androgens for proliferation and survival. To improve the patients' quality of life and possibly delay the development of resistance, intermittent androgen suppression (IAS) therapy can be given rather than continuous therapy. We consider a mathematical model of IAS therapy involving tumour cells, androgen, and the biomarker prostate-specific antigen and investigate parameter estimation with clinical data. Specifically, we implement iterative weighted least squares inverse problems to investigate the patient-specific parameters that can be confidently estimated.

Modelling of dynamic cellular and sub-cellular systems / 341

A mathematical analysis of aerobic glycolysis triggered by glucose uptake in cones

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Photoreceptors are cells in the retina that convert light to chemical signals. To offset the extreme optical and metabolic demands, and thereby prevent the toxic effects of accumulated photo-oxidative products, photoreceptors undergo renewal and periodic shedding of their outer segment (OS) discs. The OS are a substructure that carries the light sensitive molecule, opsin. People afflicted with diseases such as Retinitis Pigmentosa (RP) and Age-Related Macular Degeneration (AMD) experience a decline in vision due to photoreceptor degeneration. When photoreceptors degenerate, the shedding and renewal is interrupted eventually resulting in the disappearance of the OS and followed by the death of the cells. Currently there is no cure for diseases linked to photoreceptor degeneration. Motivated by photoreceptor degeneration, in particular RP which is typically categorized by a loss of rods (carriers of the faulty gene) followed by the loss of healthy cones, we focus our efforts on understanding the mechanisms necessary for cone survival. In an effort to begin to unravel the key process in photoreceptor functionality and vitality, this work considers key cone metabolic processes in a healthy retina. Recently it was discovered that the protein Rod-derived Cone Viability Factor (RdCVF) preserves the cones by stimulating aerobic glycolysis and accelerating the uptake of glucose needed for OS renewal and vitality in cones. Utilizing this understanding we developed a nonlinear system of ordinary differential equations to mathematically model molecular and cellular level interactions. We qualitatively validate the model and use uncertainty and sensitivity analysis to identify the processes and mechanisms that are crucial for cones vitality and functionality. Our result indicate that when all processes are functioning properly changes in key parameters at the subcellular level as well as the cellular level can significantly affect the cone population. Our analysis additionally examined the role of inefficient glucose use by the cones as well as restricted availability of RdCVF has on the overall cone populations. These results can lead to important insight into the design of new experiments such as the particular experiments that give the most valuable information, and at what time point a particular process (defined by a parameter) should be altered to increase the vitality of the cones.

Modelling of dynamic cellular and sub-cellular systems / 245

Optimal control of MANF to prevent apoptosis in Retinitis Pigmentosa

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Protein misfolding is one of the major causes of apoptosis in Retinitis Pigmentosa, where apoptosis is programmed cell death. Mesencephalic-Astrocyte-derived-Neurotrophic Factor (MANF) is a protein that has been shown to correct protein misfolding, thus reducing the death of cells due to "cell suicide". In this talk, we formulate an optimal control problem that incorporates MANF treatment to rescue photoreceptors in the eye. Numerical results are shown and discussed.

Modelling of dynamic cellular and sub-cellular systems / 340

Optimal control in a pharmacokinetics/pharmacodynamics model of doripenem

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Pharmacokinetics (PK) describes a drug's affect on a medium (such as bacteria or tumours) while pharmacodynamics (PD) describes how a drug moves throughout and is processed by the body (along with changes in drug concentration). Taken together, these models are known as PK/PD models and ordinary differential equations (ODE) are used to describe the system. We consider an existing model in the literature of the drug doripenem affect on the bacteria *P. aeruginosa* that considers the count of bacteria and resting bacteria in the central and peripheral compartments of the body. Dosing strategies tend to differ depending on the disease being treated; however, a consistent factor in treatments is an administration of 500mg for one hour, every eight hours. Treatments of this nature tend to reach concentration levels of 50mg/ml, before tapering off. Exceeding the 500mg dose brings increased risk of seizures, among other dangerous side effects including headaches, nausea, diarrhea, rashes, phlebitis, and anemia. We use control theory to search for an optimal dosing strategy and compare the results to that of the standard every-eight-hours administration. Our results show that the amount of drug needed in the control case is considerably less compared to standard dosing and that we can easily find situations in which the same amount of drug administered in the standard way will not kill the bacteria but administered in the optimal manner will kill the bacteria. This has potential significance in the case of immune compromised patients that may not be able to tolerate a standard dosing strategy.

Modelling the neuromechanics of swimming, flying and pumping systems / 18

No flows in vein: blood, oxygen, and pumping - oh my!

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From heart tubes to respiratory breathing, many organisms use valveless pumping mechanisms for internal flow transport. These pumping mechanisms were first seen in basal chordates, e.g., tunicates, where the drove through their open circulatory systems. As evolution took its course these pumping techniques begun to be found in insect hearts and during first stage of vertebrate heart development, when the heart is nothing more than a valveless tube. However, valveless pumping is not unique to only circulatory systems; some anthropods, such pycnogonids (sea spiders) use it for respiratory purposes as well. In this talk we will use fully-coupled fluid-structure interaction models to explore various valveless pumping techniques and their implications for internal flows produced across a variety of organisms and biological scales.

Modelling the neuromechanics of swimming, flying and pumping systems / 395

The emergence of neuromechanical resonance in jellyfish locomotion

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In order for an organism to have an robust mode of locomotion, the underlying neuromuscular organization must be maneuverable in a changing environment. In jellyfish, the activation and release of muscular tension is governed by the interaction of pacemakers with the underlying motor nerve net that communicates with the musculature. This set of equally-spaced pacemakers located at bell rim alter their firing frequency in response to environmental cues, forming a distributed mechanism to control the bell's muscular contraction. When turning, pacemakers induce an asymmetrically timed contraction with the bell musculature. In this work, we explore the control of neuromuscular activation with a model jellyfish bell immersed in a viscous fluid and use numerical simulations to describe the interplay between active muscle contraction, passive body elasticity, and fluid forces. The fully-coupled fluid structure interaction problem is solved using an adaptive and parallelized version of the immersed boundary method (IBAMR). This model is then used to explore the interplay between the speed of neuromechanical activation, fluid dynamics, and the material properties of the bell.

Modelling the neuromechanics of swimming, flying and pumping systems / 447

Tiny insects clap and fling with flexible wings

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Very small insects that are 1 mm in length or less, such as thrips and fairyflies, often clap their wings together at the end of each upstroke and fling them apart at the beginning of each downstroke. This 'clap and fling' motion augments the lift forces generated during flight, but very large forces are required to clap the wings together and to fling the wings apart. As the opposing forces acting normal to each wing nearly cancel during the fling, these large forces do not have a clear aerodynamic benefit. In this presentation, a standard and a elastic version of the 3D immersed boundary method is used to simulate clap and fling at the low Reynolds numbers characteristic of the smallest insects ($Re < 10$).

Modelling the neuromechanics of swimming, flying and pumping systems / 167

Effects of mechanosensory feedback on swimming behaviour and stability of a flexible body

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The lamprey is an eel-like organism used as a model for both neurophysiology and locomotion studies. Like other animals, the lamprey moves through the use of a neural network called a central pattern generator to generate a rhythmic signals down the body, inducing muscle contractions. This

signal is adjusted through information using mechanosensors (edge cells) which detect changes to the body to improve performance. Here we present a computational swimming lamprey driven by a central pattern generator (CPG) modelled as a chain of coupled oscillators. The exact functional form of feedback from the edge cells to the CPG is not known. Using the CPG to drives muscle kinematics in fluid-structure interactions implemented in an immersed boundary framework to produce the emergent swimming mode, we can examine the effects of different proposed functional forms of sensory feedback information. Effects of feedback to the neural activation on swimming performance are estimated and examined.

Models for chronic immune lesions: Lessons from atherosclerosis and tuberculosis / 123

Arterial remodelling in atherosclerosis

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The arterial wall is composed of three distinct layers: the innermost intima, the media, and the adventitia. Atherosclerosis is an inflammatory disease of the artery characterized mainly by an expansion of the intima. In 1987, Seymour Glagov quantified arterial remodelling as atherosclerosis progressed. He found that the remodelling occurred in two stages: first a compensatory phase in which the lumen maintained its size, followed by a negative remodelling phase in which the lumen cross-sectional area decreased. To date, the exact mechanisms responsible for this behaviour have not been elucidated.

In this talk I will discuss a three-layer mechanical model based on a theory of morphoelastic growth and hyperelasticity. I will present a 1D axisymmetric model that can explain Glagov Remodelling in humans and intimal thickening in animals, and a generalization to 2D which is solved using finite elements.

Models for chronic immune lesions: Lessons from atherosclerosis and tuberculosis / 133

Modelling tuberculosis granulomas – chronic immune lesions in the lung

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Tuberculosis (TB) is the number one cause of death world-wide due to infection. 2 billion are infected and 10 million die each year. Understanding the immune response to TB is crucial to developing vaccines and improving treatment strategies. The immune response to infection with *Mycobacterium tuberculosis* (Mtb), the bacteria that causes TB, results in the formation of granulomas, spherical lesions, physically containing while immunologically restraining the bacteria. These lesions are a collection of immune cells, bacteria, dead tissue and other products including lipids, which serve as a food source and oxygen products. Two key adaptations of Mtb are a non-replicating phenotype and accumulation of lipid inclusions in response to hypoxic conditions. To explore how these adaptations influence granuloma-scale outcomes in vivo, we present a multiscale in silico model of granuloma formation in tuberculosis. We build on an Agent-based model, GranSim, that we have been curating continuously since 2004 and include a flux balance model (FBM) describing the metabolism of Mtb within GranSim creating a multi-scale model. The model comprises host immunity, Mtb metabolism, Mtb growth adaptation to hypoxia, and nutrient diffusion. We calibrated our model to in vivo data from nonhuman primates and rabbits and apply the model to predict Mtb population

dynamics and heterogeneity within granulomas. We found that bacterial populations are highly dynamic throughout infection in response to changing oxygen levels and host immunity pressures. Our results indicate that a non-replicating phenotype, but not lipid inclusion formation, is important for long-term Mtb survival in granulomas.

Models for chronic immune lesions: Lessons from atherosclerosis and tuberculosis / 183

A multiphase spatial model for HDL-assisted stabilisation of early atherosclerotic plaques

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Atherosclerosis is among the leading causes of death worldwide due to its implication in heart attacks and strokes. The disease is characterised by the localised thickening of artery walls due to the buildup of fatty cholesterol-filled streaks. A key factor in determining whether an atherosclerotic plaque becomes problematic is the interplay between low density lipoprotein (LDL) and high low density lipoprotein (HDL), which are responsible for transporting cholesterol around the body. LDL is pro-atherogenic and its buildup in the artery wall will trigger an immune response whereby the recruited immune cells become engorged on lipid and remain in the artery wall. HDL in contrast has the atheroprotective properties of enabling lipid export and the egress of immune cells from the plaque. Plaque dynamics consist of many nonlinear interactions between various cellular and biochemical species including the interactions between immune cells and lipoproteins.

In this talk, we present a multiphase PDE model for an early stage atherosclerotic plaque. The model accounts for interactions between macrophages, apoptotic cells, and lipids. We model the plaque on a 1D domain with a moving boundary. Our model is based on a multiphase framework, and incorporates the effects of cell crowding by having the domain expand or contract according to the total amount of material in the plaque. We discuss how this model gives insight into how early plaque growth and regression depends on the levels of LDL and HDL in the bloodstream, and the roles of foam cell egress and HDL-enabled reverse cholesterol transport in slowing plaque growth and preventing the accumulation of potentially problematic levels of apoptotic material.

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Coagulation-fragmentation dynamics in macrophage populations

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Inflamed tissues are densely populated with macrophages that influence the balance between inflammation amplification and resolution. Macrophages that accumulate immunogenic substances such as cholesterol (in atherosclerosis) and uric acid (in gout) become pro-inflammatory and drive inflammatory responses that never resolve.

I use *in vitro* experiments to show that substances dynamically accumulate within macrophage populations via a coagulation-fragmentation process. This informs a coagulation-fragmentation equation that models macrophage accumulation of substances *in vitro*. This model generalises to a non-local

PDE model of macrophage populations during tissue homeostasis and inflammation. Model analysis shows that immunogenic substances coalesce to extraordinarily large quantities inside macrophages during tissue inflammation but not homeostasis.

Atherosclerosis is considered as a specific example. The model is used to understand the dynamics of lipid accumulation inside macrophages that populate the inflamed artery wall. Our model can simply explain several complex hallmarks of atherosclerosis disease progression such as the formation of lipid-loaded macrophage foam cells and extracellular pools of necrotic debris.

Multiscale modelling and simulation / 215

Patch dynamics for fluid flow through long narrow tubes

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Patch dynamics is a numerical multiscale solver which constructs a macroscale solution of a microscale system by solving the original microscale problem, but only within discrete patches. These patches are spread across the domain of the system and are separated by the desired macroscale spacing, thus providing a description of the system at the macroscale. The space between the patches is unsimulated, which reduces the size of the problem and permits a reduction in computational time. For the patches to accurately capture the macroscale behaviour of the system, the patches must be coupled across the unsimulated space. In developing patch dynamics, one of the main tasks is to ensure the patch coupling is both accurate and efficient. We consider the example of the flow of fluid, such as blood, through a long narrow tube with fixed obstructions. We show how to apply patch dynamics to obtain an accurate description of the fluid flow over long space and time scales.

Multiscale modelling and simulation / 193

Bimolecular reactions in the cell membrane exhibit switch-like behaviour with respect to diffusivity and molecular reach

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Many T cell receptors have long, unstructured cytoplasmic tails that contain tyrosine sites. These sites can serve as regulators of receptor activation when phosphorylated or dephosphorylated, while also serving as docking sites for cytosolic enzymes. We coarse-grain the effective interaction between two tails, and develop a mesoscopic particle-based stochastic reaction-diffusion model to study the combined diffusion of individual receptors within the cell membrane, and chemical reactions between proteins bound to receptor tails. The model suggests a switch-like behaviour in the dependence of the fraction of activated receptors on both receptor diffusivity, and on the molecular reach at which two receptor tails can interact. A simplified, analytically solvable model is developed to approximate the more complicated multi-particle system, and used to illustrate how the switch-like behaviour appears.

Multiscale modelling and simulation / 384

Lattice-free chemical reactions with multiple time scales.

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In many biological applications, it is useful to model chemical reactions at the level of individual molecules whilst not running costly Brownian dynamics models. Modelling chemical reactions as interactions at a distance can lead to errors if multiple species and time scales are important to the kinetics (for example, catalytic reactions). Multiple time scale analysis of equivalent mean-field kinetics can lead to high order reactions which are not just governed by the law of mass-action but also nonlinear kinetics such as Michaelis-Menten kinetics. In this talk we will discuss some particle-based methods which recapitulate these high order kinetics.

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Parallel stochastic simulation of cell-cell communication with spatially resolved reaction-diffusion kinetics

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Stochastic simulations are essential to the study of biological cells, yet there is no computational framework allowing for detailed spatial simulations of genetic regulatory network within large populations of cells.

We fill this gap by developing a parallel simulation framework capable of spatially resolved stochastic simulation of cell-cell signalling in multicellular systems. We use an operator-splitting method to decouple the internal reaction-diffusion kinetics from the interactions on the cells' boundaries and allow for efficient and horizontally scalable simulations of large numbers of interacting cells. Our framework is highly compatible with many existing methods and allows for hybrid simulation where both coarse and detailed models are considered at the same time. It is also greatly versatile and is deployable on various high performance computing platforms, such as clusters or clouds.

We use a small test model to study the convergence of our method as well as larger models to demonstrate weak scalability.

Our method demonstrate the feasibility of detailed stochastic simulations of large populations of interacting cells and is the first step toward more complete simulations including both detailed reaction-diffusion simulations and cell mechanics.

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Mechanisms driving 3D self-organisation of eukaryotic genomes: a systems biology approach

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The three-dimensional structure of eukaryotic genomes is non-random, dynamic, highly regulated, and can be observed to change according to external signals and differentiation state. Disruptions can lead to disease, in which incorrect genomic contacts are responsible for mis-regulation of gene expression. However, the underlying mechanisms that organise the genome are still largely unknown. While most studies focus on the activity of specific proteins which connect two chromatin loci, we seek to understand how the cells makes use of its entire complexity and of physical mechanisms. Using stochastic polymer simulations, which are informed by the analysis of large datasets and verified by quantitative experiments in budding yeast, we discovered a fundamental mechanism: The mobility of the chromatin fibre is not uniform, but heterogeneous, along its length, as a result of the unequal distribution of proteins binding along the genome. This leads to thermodynamically driven self-organisation, which we observe experimentally. It achieves spatial clustering of poised genes and mechanistically contributes to the directed relocalisation of active genes to the nuclear periphery upon heat shock (bioRxiv 106344). I will discuss the implications and present follow-up studies that make use of polymer and particle-based simulations to discover an additional layer of genome organisation.

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Multiscale methods for modelling intracellular processes

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I will discuss mathematical and computational methods for spatio-temporal modelling in molecular and cell biology, including all-atom and coarse-grained molecular dynamics (MD), Brownian dynamics (BD), stochastic reaction-diffusion models and macroscopic mean-field equations.

Microscopic (BD, MD) models are based on the simulation of trajectories of individual molecules and their localized interactions (for example, reactions). Mesoscopic (lattice-based) stochastic reaction-diffusion approaches divide the computational domain into a finite number of compartments and simulate the time evolution of the numbers of molecules in each compartment, while macroscopic models are often written in terms of mean-field reaction-diffusion partial differential equations for spatially varying concentrations.

I will discuss the development, analysis and applications of multiscale methods for spatio-temporal modelling of intracellular processes, which use (detailed) BD or MD simulations in localized regions of particular interest (in which accuracy and microscopic details are important) and a (less-detailed) coarser model in other regions in which accuracy may be traded for simulation efficiency [1,2,3]. I will discuss error analysis and convergence properties of the developed multiscale methods, their software implementation [4] and applications of these multiscale methodologies to modelling of intracellular calcium dynamics [5], actin dynamics [6,7] and DNA dynamics [8]. I will also discuss the development of multiscale methods which couple MD and coarser stochastic models in the same dynamic simulation [3,9].

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Physiologically based modelling of circadian dynamics of melatonin and its metabolite aMT6s

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Background and Objectives: The central circadian clock in the hypothalamus controls 24 hour rhythms in the human body, from sleep and alertness, to mood, metabolism, and immune response among many others. Knowledge of the phase of the clock is central to design of treatments for circadian rhythm disorders, including shiftwork disorder, jetlag, delayed sleep-wake phase disorder, and non-24-hour sleep-wake rhythm disorder. Melatonin concentrations in plasma and saliva, and the excretion rate of the major urinary melatonin metabolite, 6-sulfatoxymelatonin (aMT6s), are often used as markers of circadian phase. The relationship between these markers is complex, and measuring melatonin or aMT6s can be impractical, however, so quantitative models would prove useful to aid experimental procedures or to design treatments. Here a unified model of arousal and melatonin dynamics is presented that predicts the rhythms of melatonin and aMT6s in multiple body fluids under varying light, sleep, and circadian misalignment conditions.

Methods: We used an established model of arousal dynamics in which ordinary differential equations simulate the flip-flop switch between the sleep- and wake-active neuronal populations, and a dynamic circadian oscillator accounts for the effect of light exposure on circadian phase. This model is extended to incorporate the circadian-controlled production of melatonin in the pineal gland, its dynamics in the blood and saliva as well as its conversion to aMT6s, and ultimate excretion. Importantly, the model also includes suppression of melatonin synthesis by light exposure, which is a key confounding factor in experiments.

Results: The model predicts melatonin levels over the sleep-wake/dark-light cycle and enables prediction of widely used melatonin-based circadian phase markers, such as dim light melatonin onset (DLMO) and aMT6s acrophase under conditions of both normal sleep and circadian misalignment. The model is tested against data from ten published experimental studies, including real-world shiftwork studies, and is found to quantitatively reproduce the key features of melatonin and aMT6s dynamics, including the timing of release, peak concentrations, and response to controlled lighting.

Conclusions: Our model is the first to quantitatively predict the relationship between light exposure, circadian phase, melatonin, and aMT6s dynamics, and successfully reproduces experimental data from a variety of experiments.

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Predicting the regulation of circadian rhythms by RNA methylation

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Eating behaviour is known to influence our sleep-wake cycle, and the mechanism remains elusive. We have focused on RNA methylation that possibly connect metabolic and circadian systems. Recently, RNA methylation inhibition was found to elongate circadian period by as-yet-unknown mechanism. Since the regulatory network for circadian rhythm has been studied well, modelling can be a powerful tool for predicting the mechanism. Our study aimed at predicting possible mechanisms by which RNA methylation regulates circadian rhythm using a computational model and also a simpler model [1]. To predict the mechanism, we used information from our experimental collaborators: (1) RNA methylation inhibition stabilizes enzymes, important for circadian rhythms, (2) there are many modification processes presumably activated by the enzymes. Based on experimental data, we predicted the most likely process that is activated by the enzymes and then by RNA methylation inhibition. The prediction was confirmed experimentally by our collaborators.

[1] Kurosawa *et al.* 2017 *PLoS Comp Biol*

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Programming human sleep/wake patterns in the real-world: emergent patterns from simple rules

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Maintaining regular and sufficient sleep is important to many aspects of human health. Mathematical models of human sleep/wake patterns have typically been trained against highly regular, prescribed schedules in healthy individuals under laboratory conditions or idealized versions of real-world work schedules. Consequently, most models are deterministic and do not capture measured inter-individual variability or intra-individual variability in sleep/wake timing and duration. We extended a mathematical model of human sleep/wake patterns to incorporate aspects of real-world schedules. The model was based on the neurophysiological circuits in the brainstem and hypothalamus that regulate sleep/wake patterns, including the circadian clock and its response to light. Three simple additions to the base model were made: (i) Constraints on sleep times, representing weekly work and social constraints; (ii) Self-selection of light patterns, including exposure to natural light sources if awake during daytime and artificial light sources if awake during nighttime; (iii) Day-to-day variability in sleep onset tendency, reflecting tendency to persist with engaging behaviours (or to ruminate in insomnia) close to bedtime. From these simple rules emerged key quantitative properties of real-world sleep patterns, including: (i) Social jet-lag (i.e., mismatch between weekday and weekend sleep times); (ii) Inter-individual and intra-individual variability in sleep timing and duration, including pathological cases such as insomnia; and (iii) Challenges adapting to certain phases of rotating shift-work schedules. These findings indicate that, although human behaviour is highly complex, individual-level and population-level sleep/wake patterns can be largely recapitulated by simple rules applied to physiologically based models.

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Mathematical modelling for pharmacological manipulation of primate's circadian rhythm and precision medicine for advanced sleep phase disorder

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Circadian (~ 24 h) rhythms can be synchronized to the earth's 24 h periodic environment through external cues such as light - dark (LD) cycle. The misalignment of circadian timings with the external environment can lead to crucial physiological problems, such as jet lag, bipolar disorders and cancer. To treat the misalignment problem, we investigate the pharmacological manipulation of circadian phase of primates, *Cynomolgus* monkeys using the casein kinase1 δ/ϵ inhibitor, PF-670462. Surprisingly, we observed that the PF-670462-induced phase shift of primates (diurnal species) is less than that of mice (nocturnal species) under LD while that of primates is larger than that of mice under DD. To understand this unexpected phenomenon, we used mathematical modelling and found that the light sensitivity of primate's circadian rhythm depending on circadian phase is different to that of mouse's circadian rhythm. Furthermore, the PF-670462-induced phase shift is dramatically different depending on dosing amount and timing, light condition and chronotype. Thus, it is challenging to identify the dosing amount and timing to induce a desired phase shift. Here, we found a simple strategy to identify personalized dosing amounts and timing regardless of season and chronotype to treat advanced sleep phase disorder using mathematical modelling.

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Dead zone formation by negative feedback loops in the circadian clocks

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Circadian clocks of many organisms consist of cell autonomous rhythms of gene expression in a pacemaker tissue. Negative feedback loops in clock gene regulation are responsible for the generation of the expression rhythms. One of the characteristics of the circadian clock is its phase responses to light input signals. A light signal changes the rates of biochemical reactions in the negative feedback loops and causes a phase shift depending on the state of the clock. The phase response curve (PRC) for short light stimulations in various organisms revealed the following features. A light pulse at

morning advances the phase of the clocks, while a light pulse at evening delays the phase. Remarkably, light input signals cause only slight phase shifts during the day. Such time window where the phase of the circadian clock is insensitive to a light signal is referred to as dead zone. Several previous theoretical studies revealed that the presence of a dead zone in the PRC increased the robustness of the circadian clock. However, it remains unclear how a dead zone arises in the negative feedback loop underlying rhythmic gene expression. Here we reveal mechanisms that can produce the dead zone in the PRC using phase sensitivity analysis for Goodwin-type models. When light signals enhance degradation of repressor proteins such as TIMELESS in *Drosophila*, the cancelation of subsequent changes in transcription is critical for the dead zone formation. The influence of light signals can be nullified during the day, if the levels of repressor proteins are close to zero and transcription rate is already saturated. In contrast, when light signals induce transcription of clock genes like *Periods* in mammals, the saturation of translation of repressor protein can create a dead zone by removing the influence of excess amount of mRNA induced by the light signals. Taken together, our results suggest that the saturation of biochemical reactions in the negative feedback loops would be an underlying principle for a dead zone formation, regardless of the differences in how light signals modulate biochemical reactions in the clocks for different organisms.

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Modelling the mammalian circadian clock: from molecular mechanism to sleep-wake cycle disorders and jet lag

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Circadian rhythms originate at the cellular level from feedback processes in genetic regulatory networks. Based on experimental observations, computational models of have been proposed for the molecular mechanism of circadian rhythms, which occur spontaneously with a period of the order of 24 h in all eukaryotic organisms, as well as in cyanobacteria. Mathematical models were initially proposed for circadian rhythms in *Drosophila* and *Neurospora*, and were later extended to the mammalian circadian clock [1]. The mammalian clock model, based on the intertwined positive and negative regulatory loops involving the *Per*, *Cry*, *Bmal1*, *Clock* and *Rev-Erb* genes, can give rise to sustained circadian oscillations of the limit cycle type. These oscillations correspond to circadian rhythms spontaneously generated by suprachiasmatic nuclei and some peripheral tissues. The results pertain not only to the molecular bases of circadian rhythms but also to physiological disorders of the sleep-wake cycle linked to perturbations of the human circadian clock [2]. Among such disorders are the familial advanced or delayed sleep phase syndromes, and the non-24 h sleep-wake syndrome associated with a loss of entrainment of the circadian clock by the periodic environment. Jet lag that follows delays or advances of the circadian clock can also be studied by means of a computational approach. The latter reveals the existence of critical conditions which might considerably slow down circadian clock recovery after jet lag [3].

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Multiscaling methods and parameter inference in stochastic biochemical networks / 95

Statistical inference for parameters of biochemical networks

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The inference for the reaction rates in chemical networks is often challenging due to intrinsic and extrinsic biological noise, missing data and lack of experimental reproducibility. The talk will provide an overview of some recent work on new efficient methods of rates estimation in stochastic biochemical networks both at molecular and population scales. Stochastic SIR and Michaelis-Menten models will be used as examples to illustrate broader points.

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Function central limit theorem for Susceptible-Infected process on configuration model graphs: Further insights into the accuracy of the correlation equations

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We study a stochastic compartmental susceptible-infected (SI) epidemic process on a configuration model random graph with a given degree distribution over a finite time interval. We split the population of graph nodes into two compartments, namely, S and I, denoting susceptible and infected nodes, respectively. In addition to the sizes of these two compartments, we study counts of SI-edges (those connecting a susceptible and an infected node), and SS-edges (those connecting two susceptible nodes). We describe the dynamical process in terms of these counts and present a functional central limit theorem (FCLT) for them when the number of nodes in the random graph grows to infinity. To be precise, we show that these counts, when appropriately scaled, converge weakly to a continuous Gaussian vector semimartingale process in the space of vector-valued càdlàg functions endowed with the Skorohod topology. Based on the results obtained, we further investigate the accuracy of the so-called correlation equations from ecology literature. We show that for a certain class of degree distributions, called Poisson-type (PT) distributions, the pair approximation approach is exact in the sense that it correctly estimates the limiting first order moments of the various count variables.

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An accurate and efficient estimation of enzyme kinetics using Bayesian approach

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Characterizing enzyme kinetics is critical to understand cellular systems and to utilize enzymes in industry. To estimate enzyme kinetics from reaction progress curves of substrates, the Michaelis-Menten equation has been widely used for a century. However, this canonical approach works in a

limited condition such as a large excess of substrate over enzyme. Even when such condition is satisfied, identifiability of parameters is not guaranteed, and criteria for the identifiability is often not easy to be tested. To overcome these limits of the canonical approach, here we propose a Bayesian inference based on an equation derived with the total quasi-steady state approximation. Estimates obtained with this approach have a little bias for any combination of enzyme and substrate concentrations in contrast to the canonical approach. Furthermore, with our new approach, an optimal experiment leading to maximal increase of the identifiability can be easily designed by simply analyzing scatter plots of estimates. Indeed, with this optimal protocol, kinetics of diverse enzymes with disparate catalytic efficiencies such as chymotrypsin, fumarase and urease can be accurately estimated from a minimal number of experimental data. A Bayesian inference computational package that performs such accurate and efficient enzyme kinetics is provided in this work.

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Quasi-steady-state approximations in the stochastic models of enzyme kinetics

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In this talk I will introduce several quasi steady-state approximations (QSSAs) applied to the stochastic enzyme kinetics models. Different assumptions about chemical species abundance and reaction rates lead to the standard QSSA (sQSSA), the total QSSA (tQSSA), and the reverse QSSA (rQSSA) approximations. These three QSSAs have been widely studied in the literature in deterministic ordinary differential equation (ODE) settings and several sets of conditions for their validity have been proposed. By using multiscaling techniques for stochastic chemical reaction networks, these conditions for deterministic QSSAs largely agree with the ones for QSSAs in the large volume limits of the underlying stochastic enzyme kinetic networks. I will illustrate how our approach extends to more complex stochastic networks like, for instance, the enzyme-substrate-inhibitor system. This is joint work with Wasiur Khuda Bukhsh, Heinz Koepl, and Grzegorz Rempała.

Multistrain models & resistance / 7

Evolution of host defence in response to fluctuating environments: a theoretical and experimental study

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Environmental fluctuations, such as those caused by seasonality, are common, and climate change is expected to increase the amplitude of environmental oscillations. Therefore it is important to understand how increasing the amplitude of environmental oscillations will affect evolutionary processes, and in particular host-parasite evolution, where the extent of evolution is likely to be altered.

Here I present results from a mathematical study of host defence evolution to parasitism when the host birth rate is time-dependent. I show how the amplitude and period of seasonality affect the evolution of the host population, and how this depends on other life-history parameters, most notably the recovery rate. I also present experimental results from a study of the bacteria *Pseudomonas fluorescens* SBW25 and its phage parasite (SBW25 Φ 2), and link these to predictions from the mathematical model.

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Ecological and evolutionary dynamics of multi-strain, drug-resistant systems

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The growing threat of antimicrobial drug resistance presents a significant challenge not only to the medical community, but the wider general population. Alarming, resistant strains of infectious diseases are already endemic in many communities – particularly in developing countries and lower socio-economic settings – with new strains, which enjoy even more extensive resistance, continually emerging.

To examine this imminent threat to public health worldwide we implement a class of coupled, multi-strain epidemic models designed to simulate the emergence and dissemination of mutant (e.g. drug-resistant) pathogen strains. In particular, we investigate the ecological and evolutionary properties of a general class of multi-strain systems to determine e.g. the necessary and sufficient conditions for strain replacement/invasion, the relative contributions from amplification and primary transmission to the overall disease burden and the timescales involved. We also consider the evolutionary processes of various pathogens and investigate the rates at which both virulence and resistance evolve. This final point in particular predicates concerns about the ongoing arms race between the evolution of resistance and the development of novel treatments to treat new exotic strains – which many fear is being won by the former.

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A general stochastic model for evolutionary dynamics of communicable diseases

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Infectious diseases undergo evolutionary changes as they spread and persist in populations. Different diseases present substantially different evolutionary dynamics, with both large-scale changes that create different strains, or more incremental shifts within a strain. In this talk, we demonstrate how a general stochastic epidemic model can be used to explain different types of evolutionary dynamics for infectious diseases. We describe how parameter choices correspond to evolutionary

processes, and how simple building blocks within the model can be combined into more complex evolutionary behaviours. We compare model outputs to observed phylogenetic data from a variety of infectious diseases, including influenza, dengue, and Ebola.

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A unified stochastic modelling framework for the spread of nosocomial infections

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Over the last years, a number of stochastic models have been proposed for analysing the spread of nosocomial infections in hospital settings. These models often account for a number of factors governing the spread dynamics: spontaneous patient colonization, patient-staff contamination/colonization, environmental contamination, patient cohorting, or health-care workers (HCWs) hand-washing compliance levels. For each model, tailor-designed methods are implemented in order to analyse the dynamics of the nosocomial outbreak, usually by means of studying quantities of interest such as the reproduction number of each agent in the hospital ward, which is usually computed by means of stochastic simulations or deterministic approximations. In this work, we propose a highly versatile stochastic modelling framework that can account for all these factors simultaneously, and analyse the reproduction number of each agent at the hospital ward during a nosocomial outbreak, in an exact and analytical way. By means of five representative case studies, we show how this unified modelling framework comprehends, as particular cases, many of the existing models in the literature. We implement various numerical studies via which we: i) highlight the importance of maintaining high hand-hygiene compliance levels by HCWs, ii) support infection control strategies including to improve environmental cleaning during an outbreak, and iii) show the potential of some HCWs to act as super-spreaders during nosocomial outbreaks.

This work is based on the manuscript López-García M, Kypraios T (2018) A unified stochastic modelling framework for the spread of nosocomial infections. *Journal of the Royal Society Interface*, under second review.

Multistrain models & resistance / 407

Administration of defective virus via bang-bang control stops dengue transmission from a calibrated population of infectious patients

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As dengue is one of the human diseases with global concern, the host-vector shuttle and the bottleneck of dengue transmission is a significant aspect to study. For the four serotypes of dengue virus within host and their transmission to the vectors, we try to capture the variability in blood viremia and antibody levels of patients and their infectiousness to mosquitoes. The present model frames the occurrence of defective virus and the virus neutralization by the immune response. In order to calibrate and characterize the intrinsic variability in a dataset, collected from large number of patients, the population of models (POMs) is an efficient and reliable technique. We sample the parameters from Latin Hypercube within the biological feasible range to build the POMs. Once the POM is well-calibrated, we build a set of control settings simultaneously for every model as a mechanism for preventing transmission in a population. We use a bang-bang type control on the administration of defective virus (transmissible interfering particles, TIPs) to the symptomatic patients in course of their febrile period.

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Modelling the spread of antimicrobial resistance in hospital

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Antibiotic resistance has become one of the major health issues in the world. It kills around 700,000 people each year worldwide, and will become even worse if no new antibiotics are developed (Nature, 2017). Therefore, serious efforts are required to prevent more severe conditions in the future. One important effort in this case is understanding the dynamics of the problem so that effective policies can be prepared. To understand the dynamics of the problem, we propose a mathematical model that describes the interaction between sensitive and resistant bacteria with human population. Here, we focus on the spread of antimicrobial resistance in the hospital environment. We assume that bacteria population can be grouped into two compartments; resistant and sensitive populations, whereas patients population can be distinguished as uncolonized patient, sensitive-colonized patient, or resistant-colonized patient. Thus, the model that we develop is a two-level population model. A sensitive bacterium can be resistant due to, e.g., interactions with resistant bacteria, gene mutation, etc. An uncolonized patient or sensitive-colonized patient can be contaminated by resistant bacteria when he/she gets contact with unsterilized medical equipment, contaminated environment, etc. We consider the cases when patients are treated and not treated with antibiotics. In the first case, even if we consider that all patients that are administered to the hospital are uncolonized, eventually all of them will become colonized by resistant bacteria from the environment after a certain time interval. Therefore, apart from applying different strategies on the use of antibiotic, hygiene of environment is also playing crucial role in controlling the spread of the resistance. We show this via stability of the disease-free and endemic equilibrium of the model. Some numerical simulations will also be presented.

Nonlinear PDE models in life and social sciences / 149

Derivation of a fluid-type continuum model for contracting actomyosin bundles.

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Starting from a detailed physical model for the interplay of actin filaments, myosin motor proteins and cross-linker proteins in a contracting cell division ring, we derive a continuum model as a short filament limit of the agent based model. The model features highly nontrivial pattern formation and traveling wave solutions and explains the aggregation of actin and myosin predicted by the microscopic model as well as the scaling properties that cause the constant rate of contraction.

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Hamilton-Jacobi equations on networks and motion flow models

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After reviewing the basics about the relation between some motion flow models (pedestrians, animals, vehicles) and a class of Hamilton-Jacobi-Bellmann equations on Networks we introduce and discuss some numerical methods for the approximation of the solution. Several tests are performed to illustrate the properties previously theoretically presented.

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An anisotropic interaction model for simulating fingerprints

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Motivated by the formation of fingerprint patterns we consider a class of interaction models with anisotropic interaction forces whose orientations depend on an underlying tensor field. This class of models can be regarded as a generalization of a gradient flow of a nonlocal interaction potential which has a local repulsion and a long-range attraction structure. In contrast to isotropic interaction models the anisotropic forces in our class of models cannot be derived from a potential. The underlying tensor field introduces an anisotropy leading to complex patterns which do not occur in isotropic models. This anisotropy is characterized by one parameter in the model. We study the variation of this parameter, describing the transition between the isotropic and the anisotropic model, analytically and numerically. We analyze the steady states and their stability by considering the particle model and the associated mean-field equations. Besides, we propose a bio-inspired model to simulate fingerprint patterns (and more general any desired pattern) as stationary solutions by choosing the underlying tensor field appropriately.

Nonlinear PDE models in life and social sciences / 273

On modelling biological network formation

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In this talk we present a mesoscopic model for natural network formation processes, acting as a bridge between a discrete and continuous network approach proposed by Hu and Cai. All models describe the pressure field and the dynamics of the conductance network under pressure force effects.

We start by presenting the different approaches and analyze their corresponding properties. We will focus on special stationary solutions of the mesoscopic model including discrete network solutions.

This involves a proper reinterpretation of the system in terms of measure valued solutions. To overcome the arising difficulties, we will also introduce an alternative formulation replacing the nonlinear Poisson equation for the pressure field in the original approach by a linear side constraint.

Nonlocal models in biology / 305

Reaction diffusion approximation for nonlocal interactions

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Recently, nonlocal interactions (spatial long range interactions) have attracted attention in many fields. Mathematical treatment of nonlocal interaction is mainly based on convolution with kernels. If the profile of a nonlocal interaction is detected by experiments, we can easily investigate how patterns are generated by numerical simulations. However, nonlocal interactions are often inconvenient for observing specific mechanisms behind the target phenomena. In response to this, we proposed a new method that could convert nonlocal interactions into a reaction-diffusion system with auxiliary unknown variables. In this talk, we will explain the method of approximation, and how to determine the parameters of the reaction-diffusion system for the given kernel shape.

Nonlocal models in biology / 140

Bumps in small-world networks

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We consider a network of coupled excitatory and inhibitory theta neurons which is capable of supporting stable spatially-localised “bump” solutions. We randomly add long-range and simultaneously remove short-range connections within the network to form a small-world network and investigate the effects of this rewiring on the existence and stability of the bump solution. We consider two limits in which continuum equations can be derived; bump solutions are fixed points of these equations. We can thus use standard numerical bifurcation analysis to determine the stability of these bumps and to follow them as parameters (such as rewiring probabilities) are varied. We find that under some rewiring schemes bumps are quite robust, whereas in other schemes they can become unstable via Hopf bifurcation or even be destroyed in saddle-node bifurcations.

Nonlocal models in biology / 146**Spatial moment models for collective cell behaviour****Authors:** Michael Plank¹ ; Rachelle Binny² ; Matthew Simpson³ ; Parvathi Haridas³ ; Richard Law⁴ ; Alex James¹¹ *University of Canterbury*² *Manaaki Whenua*³ *Queensland University of Technology*⁴ *University of York***Corresponding Author:** michael.plank@canterbury.ac.nz

Many PDE-based models of collective cell behaviour implicitly assume that the population of cells is 'well mixed'. This is called a spatial mean-field assumption. In reality, populations often have a more complex spatial structure, such as clusters and/or spatial segregation of cells. This spatial structure is both a cause and an effect of non-local interactions among cells and can make a significant difference to model predictions about, for example, cell densities and invasion speeds. I will describe an individual-based model of collective cell behaviour that is based on interactions between pairs of cells, including a novel neighbour-dependent directional bias. I will then show how a continuum approximation to the individual-based model can be derived using spatial moment dynamics. This approximation tracks important features of the population spatial structure and incorporates non-local interactions that affect processes such as movement and mortality. Finally, I will show how experimental data can be used to estimate model parameters.

Nonlocal models in biology / 371**An integrated model linking structural and dynamical properties of cortical microcircuits****Author:** Pulin Gong¹¹ *The University of Sydney***Corresponding Author:** pulin.gong@sydney.edu.au

Experimental studies have begun revealing essential properties of the structural connectivity and the spatiotemporal activity dynamics of cortical microcircuits. To integrate these properties from anatomy and physiology, and to elucidate the mechanistic links between them, we develop a cortical microcircuit model that captures a range of realistic features of synaptic connectivity. We show that the model accounts for the emergence of higher-order connectivity structures, including overrepresented three-neuron motifs and highly connected hub neurons that form an interconnected rich-club. The microcircuit model exhibits a rich repertoire of activity states, ranging from asynchronous to localized and global propagating wave states. We find that around the transition between asynchronous and localized propagating wave states, our model quantitatively reproduces a variety of major empirical findings regarding neural spatiotemporal dynamics, which otherwise remain disjointed in existing studies. These dynamics include diverse coupling (correlation) between spiking activity of individual neurons and the population, propagating wave patterns with variable speed and precise temporal structures of neural spikes. We further illustrate how these neural dynamics are mechanistically linked to the structural connectivity properties by analyzing the contributions of connectivity to neural spiking dynamics and by showing that the rich-club structure is fundamentally related to the emergence of the diverse population coupling. These findings establish an integrated account of structural connectivity and activity dynamics of cortical microcircuits, and provide novel experimentally testable predictions.

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A dynamical system model of host-pathogen interaction illustrates the role of the immune system in resilience to infection

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Traditionally the study of host response to an infection has focussed on the effect of the pathogen on host health and the ability of the host immune system to clear the pathogen. In this paradigm the host experiences an initial reduction in health (assessed by suitable metrics e.g. temperature rise, weight loss, subjective feelings of ill health) as the pathogen load in the body increases. When the pathogen load is sufficiently high, the immune response is activated and attempts to clear the pathogen. If the immune system is able to eliminate the pathogen, the host survives and returns to full or partial health. If not, the infection results in death of the host. This paradigm does not account for the potential deleterious effects of the immune response on the health of the host. While this concept has been well studied in autoimmune disorders, it has not been considered in the context of diseases caused by pathogens. Here we present a dynamical system model of the interplay between the host, pathogen and the host immune response. The work utilises an existing two-variable, nonlinear mathematical model of host-pathogen interaction [1] and supplements it with a variable describing the health of the host. The equation describing the health variable incorporates terms for self repair and interactions with the pathogen and immune response. The system gives rise to a rich set of behaviours that, in addition to the usual steady states of full host recovery or host death with unbounded pathogen growth, also includes steady states with incomplete pathogen clearance and partial recovery or host death with complete pathogen clearance. The trajectories in phase space recapitulate patterns that have been described empirically [2]. The model was parameterised against a published mouse malaria dataset [3] and found to adequately describe the observed trajectories. The model also suggested that the difference between host survival and death in the study was governed by the strength of the health-immune response interaction rather than pathogen mediated effects.

[1] H. Mayer *et al.*, *Chaos* 5(1), 1995

[2] D. Schneider, *PLoS Biology* 9(9) 2011

[3] B. Y. Torres *et al.*, *PLoS Biology*, 10.1371/journal.pbio.1002436, 2016

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Elimination dynamics of intra-hepatic malaria parasites by antigen-specific CD8+ T cells

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Malaria is an infectious disease caused by parasites from genus *Plasmodium* that kills an average of a half a million people around the world annually. *Plasmodium* sporozoites are injected to humans by mosquitoes during their probing for blood. Injected sporozoites migrate to liver and invade hepatocytes. The liver stage that lasts 7 to 10 days is a target for vaccine development for humans using antigen-specific killer CD8+ T cells. However, how CD8+ T cells kill parasites in the liver is not fully understood. Here, we investigate how the numbers of CD8+ T cells, clustering around

the rodent malaria parasite, *P. yoelii* (Py), in the mouse liver, is related to the likelihood of parasites' death. We use previously published data on the viability of GFP-expressing Py-sporozoites and the movement patterns of Py-specific T cells, obtained using intravital microscopy. The data are compared with mathematical models that incorporate different mechanisms of how T cells cluster around Py-infected hepatocytes, and T cells kill the parasite, with the ultimate goal of predicting the optimal number of T cells needed to kill the parasite in a given time period (liver stage lasts 2 days in mice). Preliminary analyses indicate that there is a functional relationship between the states of the vitality indices, which is measured as the relative intensity of the GFP of the labeled parasites, and the number of T cells near the parasites. We will present the data and alternative models that could fit and fail to fit the data to understand the underlying dynamics of the killing process. We will also outline the limitations of the current data and provide details for future experimentations with sufficient power to discriminate between alternative models.

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Unravelling the within-host dynamics of Group A *Streptococcus* infection from population-level observations of strain diversity and infection prevalence

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Group A *Streptococcus* (GAS) is a ubiquitous human pathogen composed of over 230 different molecular sequence types. GAS is responsible for a broad spectrum of diseases - from superficial infections of the skin and throat to life-threatening invasive infections and post-infection sequelae. Even though most GAS infections are mild and easily treated, GAS-related disease remains a major cause of death and disability globally. This burden is greatest in settings of poverty, including developing countries and in Indigenous populations of many developed countries. Safe and effective vaccines against GAS are urgently needed to reduce this overall burden, and reduce health inequalities.

Development of vaccines and other disease reducing strategies is currently hampered by our incomplete understanding of the within and between-host dynamics of GAS infection, immunity and transmission. Studies provide limited information on the progression of GAS disease without treatment (the natural history of disease), on the relative competitiveness of GAS strains within and between hosts, and on the immune response to GAS skin infection (the predominant infection type in many host settings where GAS disease is hyper-endemic). Assessments of these key variables are all confounded by the considerable diversity of GAS. Epidemiological studies provide relevant data on the total population prevalence of GAS infections and associated disease, in relation to the diversity of GAS strains circulating in different host populations. Meta-analyses of these studies demonstrate that the level of GAS transmission and GAS-related disease in a particular host population is positively associated with the total number of strains circulating at any one time. Specifically, studies conducted in settings where GAS disease is hyper-endemic report dozens of different circulating strains, while those conducted in low prevalence settings report circulation of only a handful of distinct strain types.

In this work, we use an individual-based model of GAS transmission to explore hypotheses about the within-host dynamics of GAS infection and immunity. Specifically, we examine the conditions that must hold with respect to within-host dynamics to generate observed population-level associations

between infection prevalence and strain diversity. Our results reveal how a positive association between these two population-level measures can emerge for multi-strain pathogens that elicit strong strain-specific immunity following infection with low to intermediate levels of cross-strain immunity protecting against re-infection. The same association between prevalence and diversity can also emerge for pathogens that elicit weak strain-specific immunity following infection, but only if they can co-infect hosts with multiple strains. Given that a strong strain-specific immune response following GAS skin infection is unlikely, we propose that co-infection is a key enabler of high levels of strain diversity in host settings where GAS disease is hyper-endemic. Our findings also suggest that development of vaccines capable of eliciting strong cross-immunity over multiple strain types will be needed to impact on the burden of GAS disease.

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Novel predictors of the treatment outcome of Hepatitis B patients treated with entecavir and lamivudine nucleos(t)ide analogues

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Hepatitis B virus (HBV) infects hepatocytes, the cells making up to 80% of the human liver mass. HBV infection disorders cellular function of these cells that eventually leads to liver cancer and high mortality of the host. Despite of the availability of prophylactic vaccine, HBV infection remains a major global health issue with more than 240 million people chronically infected worldwide. The current treatment choices are based on pegylated interferon (PEG-IFN) and nucleos(t)ide analogues. These agents can efficiently reduce HBV DNA levels by inhibiting viral replication and/or immunomodulation, however, the rate of viral elimination that can be hallmarked by the loss of viral antigens is quite low.

We analyse clinical data of decay profiles of 48 chronic hepatitis B patients treated with the nucleos(t)ide analogues, entecavir (ETV) or lamivudine (LVD). During the course of treatment, the levels of three viral products were measured in patient sera: HBV DNA, hepatitis B surface antigen (HBsAg) and core-related antigen (HBcrAg). The data was processed through a mathematical model in order to estimate the disease dynamics. Our data shows that the levels of some viral products measured prior to treatment can serve as predictors of the treatment outcome. These evidences are useful for clinicians to provide better clinical management of chronic hepatitis B.

The presentation of this project will be held in animated 3D movie format.

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Modelling drug action on parasites during blood stage Plasmodium infection.

Author: Rosemary Aogo¹

Co-authors: David Khoury²; Deborah Cromer³; Trish Elliott³; Urijah Liligeto³; Pengxing Cao⁴; James McCaw⁴; Ashraf Haque³; Miles Davenport⁵

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The artemisinins are our most effective class of antimalarials, and are the internationally recommended drugs for treating malaria. This class of antimalarials has been an important factor in reducing mortality due to malaria globally. However, the emergence of resistance to this most effective and widely used class of antimalarials threatens this progress. Despite their high efficacy the artemisinins are known to have high treatment failure when used without a longer acting partner drug. It has been proposed that this may be due to a persisting population of parasites that goes dormant and emerge after drug pressure has waned. Further, artemisinin resistant parasites have been studied and it has been found that they have an altered development pathway, which protects parasites during treatment. More recently, we have observed that a non-drug based stress can cause parasites to mature more slowly, highlighting the possibility that altering the developmental cycle is a general survival strategy of the parasite. Hence, we are interested in studying the development of parasites through their life cycle with and without treatment and to quantify how drugs perturb normal development. Here, we used a novel experimental system to track the development of malaria parasites after being exposed to different antimalarials in mice. We do this by measuring the RNA and DNA content of parasites over time. Using a Gaussian mixture model (GMM) and partial differential equations we attempt to determine what fraction of parasites had their life-cycle perturbed and whether perturbed parasites matured more slowly or not at all.

By fitting the GMM to data and simulating the PDE model, our preliminary results suggest that in the case of antimalarial drug treatment, we have two distinct parasite populations. We observed a population with arrested maturation and a second population with slower maturation compared to the untreated parasites. This work is ongoing, but preliminary results indicate that antimalarial drugs completely arrest a proportion of the exposed parasites, and alter the maturation of the surviving population.

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Optimal control rabies model between dogs and human with vaccination and sterilization in dogs.

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In this paper we investigated control optimal problem for rabies model between dogs and human with the effect of vaccination and sterilization in dogs. The functional objective is formulated to maximize susceptible classes and minimize infection classes, the cost of vaccination and sterilization in dogs population. The optimal strategy of vaccine distribution is analyzed using Pontryagin Maximum Principle.

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Dynamics of an SEQIHRVS epidemic model with partial immunity, imperfect vaccine and media coverage

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A deterministic non-linear epidemic model SEQIHRVS is proposed for the transmission dynamics of an infectious disease. Quarantine, isolation and vaccination are used as control strategies in a community with pre-existing immunity. Impact of the change in the psychological behaviour of the population on infectious force due to media coverage of disease-spreading is incorporated in the model. The dynamical behaviour of the model is analysed and important biological thresholds are derived. The existence and local stability of the disease free and endemic equilibria are explored in terms of the effective reproduction number \mathcal{R}_C . It is observed that media coverage does not affect the effective reproduction number, but it helps to mitigate disease burden by lowering the number of infectious individuals at the endemic steady state and also lowering the infection peak. It is observed that the population level impact of quarantine and isolation depend on the level of transmission by the isolated individuals. Moreover, the higher level of pre-existing immunity in the population decreases the infection peak and causes its early arrival. Critical vaccination rate, critical vaccine efficacy and threshold vaccination coverage at disease-free steady state are derived for the system. Theoretical findings are supported by numerical simulation. Normalised forward sensitivity indices are calculated for \mathcal{R}_C and state variables at endemic steady state with respect to model parameters and respective sensitive parameters are identified.

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Rural poverty: a dynamical, ecological and economic perspective

Authors: Calistus Ngonghala¹ ; Giulio De Leo² ; Mercedes Pascual³ ; Donald Keenan⁴ ; Andy Dobson⁵ ; Matthew Bonds⁶

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The rural poor generally rely on their immediate natural environment for subsistence and suffer from high burdens of infectious diseases. We present a general framework for modelling the ecology of rural poverty, focusing on the exemplar drivers: infectious diseases, renewable resources, and land-use change. Interactions between these drivers and economics create reinforcing feedbacks resulting in three possible development regimes corresponding to globally stable wealthy/healthy development, globally stable unwealthy/unhealthy development, and bistability. We show that the proportion of parameters leading to poverty is larger than that resulting in healthy/wealthy development; bistability consistently emerges as a general property of generalized disease-economic systems and that the systems under consideration are most sensitive to human disease parameters. The framework highlights feedbacks, processes and parameters that are important to measure in future studies of development, to identify effective and sustainable pathways out of poverty.

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Comparing the effectiveness of different strains of *Wolbachia* for controlling Chikungunya, Dengue fever, and Zika

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Mosquitoes infected with *Wolbachia* bacteria are less capable of transmitting dengue fever, Zika, and chikungunya and have shorter lifespan. In this talk, I present the mathematical model developed to quantify the impact of infecting wild *Aedes aegypti* and *Aedes albopictus* mosquitoes with wAlbB and wMel strains of *Wolbachia* in reducing the transmission of these diseases. The model accounts for the behaviour changes of the infectious population created by differences in the malaise caused by these diseases. The differences among the diseases, mosquitoes, and *Wolbachia* strains are captured by the model parameters for the mosquito-human transmission cycle.

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Equation and dynamics of state transition from health to leukemia

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Leukemia evolves as a complex, dynamic system of multi-dimensional generic, epigenetic and micro-environmental alterations. System biology approaches to integrate a myriad of “omics” data over the course of disease progression offer promising opportunities of tracking disease evolution and predicting trajectory. However, satisfying methods and theories to model the dynamics and interpret these time series “omics” data are still lacking.

Here we present a mathematical model to describe the development and progression of leukemia in a two dimensional state-space constructed with time series genome-wide gene expression data obtained from blood cells of a mouse model of acute myeloid leukemia. The blood cell transcriptome is then represented by a particle moving in this space and its dynamics is determined by Langevin equation. We show that the transition of the transcriptome from a health state to a leukemia state can be understood in terms of mathematically-derived inflection points and energy states which characterize the dynamic probability of leukemia development. Our approach provides a framework that may be generalized to model dynamic state-transitions for other types of cancer.

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Interpreting unfolded protein response signalling related cell death in plant cell

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Endoplasmic Reticulum (ER) is a vital part for functional protein synthesis in eukaryotic cells. ER stress is caused by over-accumulation of unfolded or misfolded proteins, which are massively produced in dysfunctional protein synthesis, in the ER lumen. For a plant cell, ER stress can be induced by various environment factors, such as abiotic stress, saline stress and heat stress. At the same time, unfolded protein response (UPR) is an essential defensive mechanism in plant cells to alleviate ER stress.

Unlike the UPR in mammalian cells, only two pathways have been identified: $IRE1\alpha/\beta$ and *bZIP28* pathway. Both $IRE1\alpha/\beta$ and *bZIP28* are ER stress sensors on the ER membrane. $IRE1\alpha/\beta$ is activated when sensing the accumulation of unfolded protein in the ER lumen and then catalyse the splicing of *bZIP60* mRNA. Spliced *bZIP60* mRNA will finally be translated to *bZIP60* transcription factor. For *bZIP28*, when activated, it will dissociate from the ER membrane and then be cleaved by protease at Golgi before turning to a transcription factor. The transcription factor *bZIP60* and *bZIP28* can then initiate the transcription of a group of UPR genes. A molecular chaperone gene *BiP* is one of the typical UPR genes and *BiP* protein can help alleviate ER stress by refolding the badly folded proteins in the ER lumen.

In recent researches, ER stress was found to be linked with plant programmed cell death (PCD). Under prolonged ER stress, plant cells would finally go to PCD by showing caspase-like activity in the cell. Additionally, more evidences were presented to link ER stress and plant PCD, one important transcription factor, NAC089, was found not only to be involved in UPR signalling (controlled by both *bZIP60* and *bZIP28*), but also could promote PCD for the plant cells. So the role of NAC089 in plant cells could potentially be the deciding factor of the cell fate. We used both experimental and computational method to further understand the UPR in plant cells and the role of NAC089 plays under ER stress. We first present the functions of cathepsin B and proteasome under ER stress, which are more evidences about the link between ER stress and plant PCD. Next, we present a novel mathematical model about the UPR signalling, including NAC089 in plant cell with ordinary differential equations (ODEs). We also use both algebraic and numerical method to analyse our UPR model.

To have an insight of the survival and PCD for *Arabidopsis*, we present our data using different experimental systems. We also show the designing of an original 'Time-Dose' matrix method for plant seedling system, which shows clear seedling phenotype difference using different ER stress conditions. Finally, we use our UPR model to compare the transcript changes with experimental data and find that our UPR model still needs improvement although it makes some promising predictions.

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Species interactions modify the spread of vector-borne pathogens independent of transmission mode

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Many pathogens are transmitted by vectors, and transmission studies traditionally focus on vector-host-pathogen interactions. However, vectors are animals that forage in complex food webs, where

they interact with individuals of many species across multiple trophic levels. These interactions might indirectly affect pathogens by altering vector fitness, movement, or feeding duration, although these effects might differ for pathogens with different transmission modes. Interactions that affect vector-host encounter rates, for example, might most strongly affect non-persistent pathogens, which attach to vector mouthparts and are transmitted quickly; interactions that affect vector feeding duration might most strongly affect persistent pathogens that require long feeding bouts for transmission. Here we addressed these knowledge gaps by developing a model to explore the impacts of interactions such as competition, predation, and mutualism on the spread of pathogens with either non-persistent or persistent transmission modes. Interactions that affected aspects of vector movement and feeding behaviour (feeding duration, vector-host encounter rates) substantially altered rates of pathogen spread, whereas interactions affecting vector fitness (births, deaths) had relatively small effects. These effects of species interactions were largely independent of transmission mode, except when interactions affected vector-host encounter rates, where effects were strongest for non-persistent pathogens. Our results suggest that including species interactions and food web structure in pathogen transmission models could greatly enhance our understanding of disease ecology.

Placeholder / 465

A mathematical model for influenza transmission of two strains in single host population

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Influenza is a famous infectious disease worldwide. The disease is caused by influenza virus strains of type A, B and C. This virus attacks the bottom of the respiratory tract and one individual can be infected repeatedly with different strain types. Thus, in certain seasons, a population may be infected by two different types of viruses. In this study, the SIS (Susceptible-Infected-Susceptible) model was built to explain the transmission of influenza by two strains in one population. The dynamic analysis will be done on this model include the existence condition and coexistence of equilibrium point and stability of endemic. Parameter estimation is also done to obtain unknown parameter value and will be discussed sensitivity analysis to parameters that influence to basic reproduction ratio.

Placeholder - Board: 89 / 302

A subnetwork-based approach for studying concentration robustness

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Disturbances in the cellular environment can lead to variations in the chemical profile of the cytoplasm and result in deviations from homeostasis that are detrimental to the organism. In response, cellular networks have evolved to be robust to such perturbations but network complexity and the elusiveness of parameter values makes analysis difficult. Studying the network topology provides a way around this by delineating families of networks capable of exhibiting robustness based solely on their structure. Nevertheless, conditions for robustness have been studied mostly in the global context of the network and it is presumed that many of these conditions remain unknown. We propose that examination of a subset of reactions within the network suffices to show the presence of robustness. In particular, if a subnetwork inherits every possible steady state from its parent network, robustness in the subnetwork will extend to the entire network. We derive conditions that

result in “steady state inheritance” for networks composed of at most two subnetworks. Additionally, we show that the steady state inheritance of one subnetwork extends to the other subnetwork as well. Lastly, we note an alternative submodule-based approach that extends robustness to the whole network based on species at the intersection of both subnetworks.

Placeholder - Board: 39 / 485

State estimators for a class of epidemiological systems

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We consider a class of epidemiological models that includes most well-known dynamics for directly transmitted diseases, and some reduced models for indirectly transmitted diseases. We propose a simple observer that can be applied to models in this class. We analyse and implement this observer in two examples: the classical SIR model, and a reduced Bailey-Dietz model for vector-borne diseases. In both cases we obtain arbitrary exponential convergence of the observer. For the latter model, we also apply the observer with real data.

Placeholder / 460

SEIVR epidemic model (Susceptible, Exposed, Infected, Vaccinated and Recovered) on the spread of hepatitis B disease

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Hepatitis B is a disease caused by the hepatitis B virus. It's generally divided into 3 categories namely healthy carrier, acute hepatitis, and chronic hepatitis. The spread of hepatitis B disease can be modelled in a mathematical model. We develop the mathematical model to describe the spread of hepatitis B. We modify the model of SEIV by introducing recovery class into the model (SEIVR model). The behaviour of the dynamics model is analyzed to investigate the positivity and boundedness solutions, and the stability of equilibrium points. Basic reproduction number (R_0) is derived from next generator matrix to determine the stability of equilibrium point and endemicity of hepatitis B disease in long term. The disease free equilibrium point is locally asymptotically stable if $R_0 < 1$, unstable $R_0 > 1$. The endemic equilibrium point is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. Simulation results are presented to provide the description of the analysis results.

Placeholder - Board: 35 / 412

A mathematical model for tuberculosis improper treatment; a case of MDR-TB and XDR-TB

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Tuberculosis (TB) is one of deadly infectious diseases. The ordinary treatment for this disease is by using antibiotics, within non stop duration of 6 months. There are many cases for many reasons, that patients receive treatment less than required duration of treatment. This condition, called improper treatment, unfortunately could lead to Multi-drug Resistant Tuberculosis (MDR-TB) which is resistant to the first line antibiotics and need a longer duration of treatment. In addition, in simplified case, the improper treatment of MDR-TB also could lead to similar case; called Extensively-drug Resistant Tuberculosis (XDR-TB). The cases of MDR and XDR-TB recently already increasing in many parts of the world. In this paper, a mathematical model that can be used to explain phenomena of MDR-TB and XDR-TB, and its simulation is presented.

Placeholder - Board: 113 / 489

Transition between reaction-controlled and diffusion-controlled regimes in stochastic reaction diffusion systems

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Over the past two decades, various modelling and simulation approaches have been proposed for stochastic reaction-diffusion processes. These include compartment-based (and event-based) algorithms such as the Next Subvolume Method (NSVM), which is based on the Reaction Diffusion Master Equation formalism, and particle-based (and time-driven) Brownian dynamics (BD) models such as Smoluchowski dynamics (Smoldyn), and Green's Function Reaction Dynamics. In this presentation, we discuss the performance of NSVM and Smoluchowski-theory based algorithms in the context of reaction-limited and diffusion-limited scenarios and further propose a hybrid NSVM-BD algorithm for the stochastic simulation of reaction diffusion systems that display both reaction-limited and diffusion-limited regimes. Through various examples we show that our algorithm is able to accurately capture both the macroscopic and the microscopic limit, simultaneously, and can also display the transition regime between the high concentration and the low concentration (or diffusive search) scenario.

Placeholder - Board: 74 / 435

Modelling the role of a sustained chloride current in rod bipolar cell sensitization

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Dim light vision relies on rod bipolar cells to relay light information from rod photoreceptors to downstream neurons in the retina. Rod bipolar cells release glutamate in proportion to their photoreceptor response-driven depolarization, but this depolarization can also be modulated by the activity of retinal interneurons. Blocking or eliminating rod bipolar cell GABA_C receptors, a specialized GABA-sensitive but non-inactivating chloride channel, drastically decreases rod bipolar cell responses and the overall sensitivity and operational range of the rod bipolar cells. We believe that this occurs due to tonic GABA_C-driven hyperpolarization of the rod bipolar cell resting potential. To test

this hypothesis, we used a conductance-based model to simulate the responses of rod bipolar cells to flashes of light under various levels of background illumination with either no, variable, or maximal rod bipolar cell chloride conductance and compared this model to experimental electroretinography data from GABA_C knockout mice, wildtype mice, or mice injected intravitreally with exogenous GABA. Our results indicate that chloride currents are used in addition to potassium currents for hyperpolarization of rod bipolar cell resting potential and provide clues for how this sustained GABA_C input from retinal interneurons might be regulated in normal dim light vision.

Placeholder - Board: 34 / 377

Dynamical system of HIV infections among female sexual workers and injecting drug users with treatment and prevention

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In this paper, a model for the human immunodeficiency virus (HIV) infection among female sexual workers and injecting drug users is formulated. The injecting drug users (IDUs) are also considered as clients, therefore there are two transmission routes considered in this model: needle sharing between IDUs and commercial sex between female sex workers and IDUs as clients. This model also incorporates a treatment for the infected population and a prevention for the susceptible population. The qualitative analysis are also presented. The local stability are obtained by analyzing the epidemic threshold R_0 . The result shows that the disease-free equilibrium is locally asymptotically stable when the condition $R_0 < 1$ is satisfied and a unique endemic equilibrium exists and it is locally asymptotically stable if $R_0 > 1$. The numerical simulations are also performed to support analytical result.

Placeholder - Board: 62 / 479

Resolving the complexity of ecological networks

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Ecosystems are often modelled as directed graphs, representing flows of conserved quantities (e.g. biomass, energy, C, N) among a set of compartments (e.g. species, detritus). Ecological networks can be fairly large and complex. Decomposing an ecosystem model into smaller sub networks for easier analysis is often tempting. However, essential ecosystem behaviour may be lost by breaking connections, excluding compartments, or clustering. Neither flows, nor compartments can function in isolation.

Motivated by flux based analysis and metabolic control analysis, we propose an alternative building block for ecological networks, called fluxes. A flux is a smaller subnetwork defined according to specific mathematical rules. In ecological terms, a flux represents the smallest process within the ecosystem that can theoretically sustain itself. This can be a material cycle within the ecosystem, or a simple foodchain in a complex foodweb. Fluxes have interesting mathematical properties that render them extremely useful for ecological representation and studies. For example, any ecological network has a unique set of fluxes, and any ecosystem model can be expressed as a linear combination of its fluxes.

Fluxes provide a unique opportunity to study complex and large ecosystems. Since no connections are lost during this mapping, system-wide properties of the full ecosystem can be studied using individual fluxes. For example, the amount of material cycling that occurs within the entire ecosystem equals the sum of material cycling that occurs within each of its fluxes. This result holds regardless of model size or complexity.

Intertidal oyster reef ecosystem model will be used to demonstrate flux decomposition via EcoNet (<http://eco.engr.uga.edu>), a free online software we have developed.

Pleiotropy, adaptation and the evolution of sex differences / 64

Modelling the evolution of sex-specific dominance in response to sexually antagonistic selection

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Arguments about the evolutionary modification of genetic dominance have a long history in genetics, dating back over 100 years. Mathematical investigations have shown that modifiers of the level of dominance at the locus of interest can only spread at a reasonable rate if heterozygotes at that locus are common. One hitherto neglected scenario is that of sexually antagonistic selection, which is ubiquitous in sexual species and can also generate the stable high frequencies of heterozygotes that would be expected to facilitate the spread of such modifiers.

I will present a recursion-equation model that shows that sexually specific dominance modification is a potential outcome of sexually antagonistic selection. The model predicts that loci with higher levels of sexual conflict should exhibit greater differentiation between males and females in levels of dominance and that the strength of antagonistic selection experienced by one sex should be proportional to the level of dominance modification. These predictions match the recent discovery of a gene in Atlantic salmon, in which sex-dependent dominance leads to earlier maturation of males than females, a difference that is strongly favoured by selection. Finally, I suggest that empiricists should be alert to the possibility of there being numerous cases of sex-specific dominance.

Pleiotropy, adaptation and the evolution of sex differences / 73

The effect of genomic imprinting on QST

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A gene is imprinted when its level of expression is dependent on the sex of the parent it was inherited from. An unusual consequence of imprinting is that male and female additive genetic variances differ, and so ignoring imprinting can lead to misspecification of a number of evolutionary parameters, including the predicted response to selection. QST - the differentiation of quantitative traits between populations - is a consequence of the combined effects of both neutral and selective forces acting across the metapopulation. QST is often compared to FST, the differentiation across populations measured at (presumably) neutral loci, in order to determine the role of selection in shaping trait divergence between populations. Previous theoretical work has demonstrated that properties of the

genetic basis of a quantitative trait, such as inbreeding, dominance and epistasis, can marginally inflate or deflate QST, although it is unlikely that any of these properties would be strong enough to “hide” the effects of strong selection. Here, we assess the effects of imprinting on QST by exploring a two-population model of migration, inbreeding, selection and imprinting. We show that imprinting is unlikely to hide the effects of divergent selection, lending further support to the general conclusion that strong selection is unlikely to be masked by inter- and intra-locus interactions. However, the magnitude of imprinting’s effect on QST is surprisingly large – ignoring imprinting, and hence the differences between male and female additive genetic variances, will lead to considerable over-estimation of the strength of selection.

Pleiotropy, adaptation and the evolution of sex differences / 297

Coadaptation of mitochondrial and nuclear genes, and the cost of mother’s curse

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Strict maternal inheritance renders the mitochondrial genome susceptible to accumulating mutations that harm males, but are otherwise benign or beneficial for females. This ‘mother’s curse’ effect can degrade male survival and fertility if unopposed by counteracting evolutionary processes. Coadaptation between nuclear and mitochondrial genomes—with nuclear genes evolving to compensate for male-harming mitochondrial substitutions—may ultimately resolve mother’s curse. However, males are still expected to incur a transient fitness cost during mito-nuclear coevolution, and it remains unclear how severe such costs should be. We present a population genetic analysis of mito-nuclear coadaptation to resolve mother’s curse effects, and show that the magnitude of the ‘male mitochondrial load’—the negative impact of mitochondrial substitutions on male fitness components—may be large, even when genetic variation for compensatory evolution is abundant. We also find that the male load is surprisingly sensitive to population size: male fitness costs of mito-nuclear coevolution are particularly pronounced in both small and large populations, and minimized in populations of intermediate size. Our results reveal complex interactions between demography and genetic constraints during the resolution of mother’s curse, suggesting potentially widespread species differences in susceptibility to mother’s curse effects.

Pleiotropy, adaptation and the evolution of sex differences / 369

Entering a virtuous cycle of niche construction

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Organisms often modify their environments to their advantage through a process of niche construction. Environments that are improved through positive niche construction can be viewed as a public good. If free riders appear that do not contribute to the shared resource and therefore do not incur any associated costs, the constructed niche may become degraded resulting in a tragedy of the commons and the extinction of niche constructors. Niche construction can persist if free riders are

excluded, for example if niche constructors monopolise the resource they produce to a sufficient degree. We suggest, however, that the problem of free riders remains because it is possible that non-niche constructors with an enhanced ability to access the resource appear and invade a population of constructors. Using mathematical models we show that positive niche construction can be maintained if it is inextricably linked to a mechanism that makes free riding costly, such as a trait that confers a benefit to only niche constructors. We discuss this finding in terms of genetic interactions and illustrate the principle with a two locus model. We conclude that positive niche construction can both evolve and be maintained when it has other beneficial effects via pleiotropy. This situation may apply generally to the evolutionary maintenance of cooperation.

Plenary / 34

What do spider monkeys, Peruvian fishing boats and sulking albatross have in common?

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Lévy walks have dominated foraging theory since they were brought to our attention in the mid-nineties. However the path to enlightenment has not been smooth. I will take you on a brief history of Lévy foraging theory that has played out in the published literature. Are they the solution to finding your keys or an ecological version of the quaternion?

Plenary / 37

The mathematics of wound healing

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The process by which a skin wound heals is complicated and requires the concerted action of a large number of cell types, chemicals and fibres. There have been many attempts to mathematically describe the wound healing process using a variety of different mathematical approaches. In this talk, I will review some of the earlier mathematical models developed for wound healing and the biological impact they have made. My own research into the mathematical modelling of wound healing is aimed at informing clinical treatment of non-healing wounds by devising governing equations which capture the essential behaviour of the complex system. In this talk I will discuss several of these mathematical models, the clinical insight gained by numerical and analytical investigation of them and the future challenges that I see in this research area.

Plenary / 65

Coupled social and ecological dynamics for ecosystem management

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For successful ecosystem management and biodiversity conservation, in addition to ecological and evolutionary processes, we need to consider social and economic influences on the management target. Here, we introduce four models that address economic and social aspects of human society in the context of ecosystem management.

1. Lake water pollution. Players choose between cooperative (but costly) option and economical option. Their decision is affected by the fraction of cooperators in the community and by the importance of water pollution problem. This social dynamics is coupled with the dynamics of lake water pollution. Oscillation of large amplitude is generated if social change occurs faster than ecosystem responses. If phosphorus is removed more effectively either from the inflow or from the lake water, the pollution level may increase (rather than decrease) due to the decline in people's willingness to cooperate (paradox of nutrient removal).
2. Herders in a southern Mongolian rangeland. Herders choose foraging sites for their animals in the dry season. If grazing pressure is very strong, the grass biomass becomes depleted and more herders choose to move their animals to an alternative rangeland. They may return to the focal rangeland when the quantity and quality of the grass improves. The system may exhibit bistability with a strong dependence on the initial condition or perpetual large-amplitude fluctuation. Implications for rangeland management are discussed.
3. Profit-sharing of plantation management. Illegal logging is a very serious threat to tropical forests. The owner chooses the age of trees to cut, and the workers choose their monitoring effort to prevent illegal logging. After the trees were removed, the owner hires workers to re-plant young trees. Under the presence of illegal logging pressure, the owner may find it profitable to share the income by selling logs with the workers to solicit their monitoring efforts.
4. Graduated sanction for common pool resource management. From field studies, E. Ostrom discovered the severity of punishment to rule deviators need to increase with the amount of harm caused by the selfish action. We conclude that graduated punishment is the most efficient way to ensure cooperation when evaluation errors are unavoidable and when the social group is heterogeneous with respect to the sensitivity of its members to utility difference.

Plenary / 534

Modelling immunity: a multi-scale problem

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Infectious diseases affect individuals (immunology) and populations (epidemiology). While these two scales of infection are intimately linked, the vast majority of studies of infectious diseases ignore or greatly simplify the effects of the other scale. As a result, public health programs can be ill-informed. Mathematical models that link the in-host and population scales of infection can better inform public health programs. However, these models can become very complex very quickly, even in their most simplified forms. We focus our mathematical modelling studies on the effects of immunity, the key outcome of infection at the in-host level (development of immune memory), and the key indicator of pathogen spread at the population level (through susceptibility and transmissibility). Immuno-epidemiological models that are well-informed by our in-host and population level studies are then developed. In this talk I will discuss our immunological, epidemiological, and immuno-epidemiological modelling studies of influenza, HIV, measles and pertussis. The effects of vaccination and waning immunity will be highlighted.

Plenary / 518

Transport network designed by current-reinforcement rule

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Network of transport is found in a wide range of living system. The typical examples are vascular network in vertebrates and tracheal network in vascular plants, and mycelial network in fungi. Such a network structure is found in self-organized colony of unicellular bacteria: a biofilm that is a sheet-like aggregate of many bacteria and sticky polysaccharides secreted from the bacteria. Comparative study of various kinds of bio-network of transport along phylogenetic tree is probably interesting since an insight into evolutionarily sophisticated designing of adaptive network is obtained in a wider perspective.

At the interface between unicellular and multicellular branches, there is an unique organism with highly flexible body shape with network structure, true slime mould Myxomycete (or Mycetozoa). *Physarum polycephalum* Schw. is a well-studied species of true slime mould in cell biology and biophysics last seventy years although several hundreds of species are known. By using this organism, comparative study of bio-network rises for the last one or two decade(s).

A kind of huge amoeboid organism named *Physarum plasmodium* constructs a intricate network of veins for circulating nutrients and signals over the entire body. The network shape (topology of connectivity, and sequence of branching in vein network, for instance) is drastically re-organized within hours in response to external conditions. The past studies showed that the network shape was optimized to maximize possibility of survival, in some senses. So we may extract an algorithm for optimal design of functional network from the primitive organism. The key thing is adaptive dynamics of current-reinforcement rule: each vein of network becomes thicker when current is large enough through the vein itself, while it becomes thinner and dies out otherwise.

We propose the equations of motion for this simple rule, and functions and formation of transport network is analyzed. We will show that the rule is applicable to the other bio-systems: (1) social dynamics of public transportation, (2) formation of network structure in porous tissues bone (bone remodelling in other words). A tractable perspective to think similarly of a variety of bio-network is given from the viewpoint of current-reinforcement rule.

Plenary / 533

Inverse and recursive approaches to discover and predict emergent behaviour in complex biosystems comprising human tissues

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Through combination of novel microscopy protocols for imaging live cells and tissues as well as experimental mechanics methods, we have begun to elucidate mechanisms underpinning emergent properties of hierarchical materials such as tissues [1,2]. We refer to the process as Microscopy Aided Design And Manufacture (MADAME). We apply this paired imaging and computational technology approach to engineer advanced materials that emulate the smart mechanical properties of tissues. These materials have applications in diverse arenas, from medical implants to the transport and sports industries. Our “bottom up” approach to emulating mechanically responsive natural

materials integrates the fields of multiscale biomechanics and mechanobiology in novel ways and underscores the role of mechanics in life. It also elucidates how “brainless” cells adapt to dynamic mechanical environments by constantly weaving and thereby adapting their own niche [3]. In addition, our connectomics approach to understanding cell networks *in situ*, in tissues as diverse as brain and bone, provides a basis for a new approach to diagnostics, predicting emergent disease states using an epidemiological approach in cell populations within individual patients [3,5,6]. Challenges to the connectomics approach include acquisition, handling and archiving of massive data sets, discrepancies in technical capacities (e.g. resolution) of imaging methods, and hard and software approaches, as well as bridging and upskilling of research teams to apply a transdisciplinary approach using innovative conceptual, experimental, and translational approaches. This talk integrates our understanding of cells, expert tissue prototypers, and their networks, to emulating cellular approaches to engineer and manufacture materials and medical devices of the future.

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Plenary / 532

Multiscale image based modelling in biology

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In this talk I will describe the application of state of the art image based modelling to several seemingly different areas of biology. I show examples from biomedical (lymphatic, vascular and lung system) and agricultural problems of plant soil interaction. I will describe the workflow from imaging (X-ray CT, XRF, SEM-EDX, histology), image reconstruction, image segmentation, computation and how to utilize this work stream to synthesise new scientific knowledge. In particular I will also outline several challenges and bottle necks in this process to hopefully encourage more mathematicians to get involved in the full pipeline.

Plenary / 531

How mathematics can be used in nature conservation

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There are now over 50 conservation science journals and the field is booming. The world's top journals, *Science* and *Nature*, routinely cover conservation science issues, but the field has been dominated by ecologists. Solving conservation problems is as much about maths and economics, as it is about ecology. Our group at the University of Queensland, and our national ARC Centre of Excellence or Environmental Decisions (CEED) has been using models and tools from operations research to formulate and solve pressing conservation problems. In this talk I will provide an array of examples of how operations research and ecological modelling has delivered outcomes for nature conservation – from locating places for national parks to saving threatened species.

Population dynamics models with broader ecological, evolutionary, and social feedbacks / 301

Separation of trait-mediated and biomass-mediated indirect effects in a system of a plant and two herbivores

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Two consumer species that share a single resource species can indirectly interact each other, even without direct interactions. A typical indirect interaction is exploitative resource competition that results from a depression of resource biomass by consumption, which can be referred to as “biomass-mediated indirect effect”. Another type of indirect interaction is called “trait-mediated indirect effect”, which is caused by changes in traits of resource species. For example, an attack from one herbivore species can either reduce biomass or induce defensive traits of the host plant individual, which may in turn suppress performance of another herbivore species on the same host. It is notable that two types of indirect effects are difficult to detect separately in nature because it is necessary to measure both reduction in biomass and changes in traits of plants and observe respective effects on herbivore performance. In order to understand the separate and joint influences of two indirect effects, we analyzed a population dynamic model of one-plant two-herbivores system, including an inducible non-specific defense of plant individuals. Our analysis revealed (1) the inducible non-specific defense can promote coexistence of three species, (2) the coexistence of three species requires reduction of population densities of both herbivores, (3) in such a case, one herbivore is controlled by biomass-mediated negative indirect effect, whereas the other herbivore is controlled by trait-mediated negative indirect effect. This indicates that both types of indirect effects need to co-occur for the coexistence of consumer species, suggesting that trait-mediate indirect effect may be as common as biomass-mediated indirect effect.

Population dynamics models with broader ecological, evolutionary, and social feedbacks / 291

When mismatches don't matter: the dynamical consequences of divergent ecological and economic scales in coastal fisheries

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Conservation management decisions are often implemented at the scale of human communities, rather than the scale of the most relevant ecological dynamics. Research frequently points out the loss in efficiency that results from such “scale mismatches”. However, the scale of management is influenced by socio-economic constraints on management actors - not all people want to cooperate with each other. While it is clear that objectives can be better achieved if management and ecological scales are aligned, it is not clear whether such benefits justify the costs of alignment, or how alignment can be achieved in multi-actor contexts.

On Manus Island in Papua New Guinea, small customary tenure areas define the scale of fisheries management decisions, but their fish stocks are connected by pelagic larval dispersal. We quantify

the extent of this scale mismatch for the serranid *Plectropomus maculatus* by empirically estimating larval dispersal distances, and integrating this data into a bioeconomic model of the multi-actor fishery, and identifying the cooperative Nash equilibrium. Larval dispersal allows individual communities to externalise the costs of overharvesting, and export the benefits of cooperative behaviour, to non-cooperating groups. Despite these mismatched scales, the communities on southern Manus have recently created a tribal network for management and negotiation, emphasising the importance of social capital in avoiding suboptimal outcomes or the need for top-down governance.

Population dynamics models with broader ecological, evolutionary, and social feedbacks / 309

Effects of interplay between direct and indirect effects on diversity of ecological communities

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Species interactions are important to determine structure and stability of ecological communities. In particular, a variety of indirect effects appear between species which do not interact directly. However, indirect effects do also appear between species that directly interact. For example, plant species sharing a common herbivore may engage in both interference competition directly with other plant species and apparent competition indirectly through common herbivores. Then, if a plant species augments herbivores, then grazing pressure on another plant species increases and decreases in biomass of the latter plant may weaken competitive pressure on the former plant species. In this way, there may appear many feedback loops in a complex ecological community where species affect each other through many different paths connecting them. Thus, we should understand interactive consequences of a direct and many indirect effects to understand structure and dynamics of ecological communities. However, studies on indirect effects tend to focus on changes in density of a target species and neglect changes in diversity of the whole community.

In this presentation, we consider a very simple dynamical system model that describes a community composed of predator, herbivore and many plant species. In this model, since predators reduce herbivores and weaken grazing pressure on plants, there appear a positive trophic cascade from the predator to plants. Then, increased plant biomass may enhance both direct interference and indirect apparent competition between plants. Therefore, it is interesting to investigate how the presence of predators affects diversity of the plant community. We analytically solve steady state solutions of the model and investigate effects of predation, grazing, and interference competition on the number of plant species and total plant biomass. Based on the results, we discuss the importance of interplay between direct and indirect effects for structure of ecological communities.

Population dynamics models with broader ecological, evolutionary, and social feedbacks / 274

Adaptive defense of a shared pest can enhance efficiency of biological control by two natural enemies

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It has long been debated whether introduction of two (or more) natural enemies results in more efficient pest control than that of either one enemy. Intra-guild predation (IGP) among two natural enemies sharing a single pest has been recognized as an important factor to reduce efficiency of pest control. While the classical theoretical model of IGP showed that introduction of two natural enemies is less efficient for pest control, empirical works have showed positive, negative, and neutral results. However, the classical IGP model did not consider any behavioural plasticity of the pest and natural enemies.

In this study, we extended the classical IGP model by considering adaptive defense by the pest and switching predation by the omnivorous natural enemy (omnivore) and examined separate and joint effects of them on efficiency of pest control. We assumed that the pest can adaptively allocate efforts toward two kinds of defense respectively against the two natural enemies to increase its own fitness, with cost of reduction in its own reproduction. Switching predation by the omnivore is expressed as the Holling's type III functional response to the pest and another natural enemy (intermediate predator). Equilibrium pest density is used as an index of efficiency of biological pest control.

If the pest employed the adaptive defense, introduction of two natural enemies performed more efficient pest control than that of either one enemy, unless the IGP was too intensive. This is because the pest allocated more defensive effort against the more threatening enemy, and thus it was difficult for the pest to simultaneously prevent predation from the two enemies. On the other hand, switching predation could not improve biological control by two natural enemies. However, the type III functional response tempted the pest to abandon defensive effort against the omnivore, because the predation pressure was negligible at low pest density and saturated at high density. Since the intermediate predator was suppressed by the undefended omnivore, defensive effort against the intermediate predator also diminished. Thus, switching predation could offset the effects of defense and the prey density could be lowered by two natural enemies even under severe IGP. Consequently, types and combination of behavioural plasticity might cause qualitatively different outcomes of biological control introducing two natural enemies.

Population dynamics models with broader ecological, evolutionary, and social feedbacks / 244

Influence of sex-specific dispersal on local sex ratio, mating success and spatiotemporal population dynamics

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Sexual dimorphism (SD), sexual differences in traits, represents one of the most remarkable source of biodiversity in the world. In most of species, two sexes play different roles in reproduction and thus are imposed by selection pressures in different forms and strengths. This explains the generality of this phenomenon and the extensive applicability of SD theory in nature. In this talk, I will provide an example demonstrating how sexual differences in the dispersal strategy can influence metapopulation dynamics. We developed a sex-structured two-patch model and specified that two sexes have different decision-making processes according to the accessibility of reproductive resources; in brief, females move to the patch with more breeding sites (i.e. carrying capacity minus local population size) whereas males move to the patch with more mating opportunities (i.e. unmated females). Such assumption is valid given that sex-specific dispersal has been commonly recorded in natural systems. Our simulation results illustrated how sex-specific dispersal increased or decreased local population size through changes in local sex ratio and individual reproductive success; notably, such results were not able to be generated through conventional, asexual metapopulation models. We advocate that incorporating the perspective of SD into population dynamic models are needed and it

can advance our knowledge of population dynamics by disclosing detailed mechanisms underlying population processes.

Population dynamics models with broader ecological, evolutionary, and social feedbacks / 437

Optimal management strategies to control mammal populations incorporating behaviourally mediated indirect effect

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Overpopulated mammal populations cause damage to agricultural crops in Japan. We need to keep population sizes at appropriate levels. When we determine management plans, we have to deal with various uncertainties such as population size, population growth rate, and agricultural damages caused by mammals due to lack of sufficient data. It is important to reduce those uncertainties and allocate hunting effort under limited budget.

Prey populations change their behaviour due to presence of predators. Predation risk could cause behavioural changes of prey such as vigilance at the cost of time spent grazing, and population growth rates of prey may decrease without predation itself (the effect is called as behaviourally mediated indirect effect). It is possible that population decline in Japan decreases negative impacts of human activities on mammal populations. In addition the agricultural damage could affect human activities. Hence it is important to incorporate the behaviourally mediated indirect effect for effective mammal managements.

We will introduce a population model incorporating a behaviourally mediated indirect effect for a management of wild boars (*Sus scrofa*) in Chiba prefecture, Japan. First we estimate population densities and population growth rates using Bayesian model averaging. Second we estimate relationship agricultural damages and population densities in heterogeneous landscapes. Last we derive optimal allocations of hunting efforts to minimize expected damages to agricultural crops. We discuss how incorporating the behaviourally mediated indirect effect is important for effective wild boar management.

Population heterogeneity and disease spread (Mathematical Epidemiology subgroup) / 132

Metapopulation epidemic model fitted to spatiotemporal spread of rubella in Japan, 2012-13

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Background: Japan experienced a nationwide rubella epidemic from 2012 to 2013, mostly in urban prefectures with large population sizes. The present study aimed to capture the spatiotemporal patterns of rubella using a parsimonious metapopulation epidemic model and examine the potential usefulness of spatial vaccination.

Methodology/Principal Findings: A metapopulation epidemic model in discrete time and space was devised and applied to rubella notification data from 2012 to 2013. Linearly approximating growth patterns in six different time periods using the particle Markov chain Monte Carlo method yielded estimates of effective reproduction numbers of 1.37 (95% CrI: 1.12, 1.77) and 1.37 (95% CrI: 1.24, 1.48) in Tokyo and Osaka groups, respectively, during the growing phase of the epidemic in 2013. The rubella epidemic in 2012 involved substantial uncertainties in its parameter estimates and forecasts. We examined multiple scenarios of spatial vaccination with coverages of 1%, 3% and 5% for all of Japan to be distributed in different combinations of prefectures. Scenarios indicated that vaccinating the top six populous urban prefectures (i.e., Tokyo, Kanagawa, Osaka, Aichi, Saitama and Chiba) could potentially be more effective than random allocation. However, greater uncertainty was yielded by initial seeds of infectious individuals, initial fraction susceptible and stochasticity.

Conclusions: While the forecast in 2012 was accompanied by broad uncertainties, a narrower uncertainty bound of parameters and reliable forecast were achieved during the greater rubella epidemic in 2013. By better capturing the underlying epidemic dynamics, possibly with age-dependent and prefecture-specific susceptibility distributions, spatial vaccination could potentially be substantially discriminated from random vaccination.

Population heterogeneity and disease spread (Mathematical Epidemiology subgroup) / 430

A general framework to account for unobserved heterogeneity in epidemiology

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Unobserved heterogeneity was introduced in 1920 as a modifier of individual hazards. The concept was termed frailty in demography to describe variation in individual longevity [1], and has been incorporated in methods for survival analysis. As the frailest individuals are removed earlier from a heterogeneous group, mean hazards appear to decrease over time – cohort selection – leading to some of the most elusive effects in population science. Despite the accumulation of documented fallacies induced by cohort selection, the issue remains largely overlooked. I will expose the ubiquity of the phenomenon and propose a general framework to infer and compare trait distributions, with examples of current interest in epidemiology and related disciplines:

- (1) Vaccines appear less effective in high-incidence settings. Are they, really [2]?
- (2) What is the real effect of *Wolbachia* on mosquito susceptibility to dengue viruses [3]?
- (3) As populations of bacteria are exposed to antibiotics, their mortality rates decline due to selection for noninherited resistance⁴. How much does this phenomenon share with what has been described in human demography [1]?
- (4) What does cohort selection add to the debate between neutral and niche theories of biodiversity?

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Population heterogeneity and disease spread (Mathematical Epidemiology subgroup) / 484

Vector feeding preference annihilates backward bifurcation and reduces endemicity

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We propose and analyze a mathematical model of a vector-borne disease that includes vector feeding preference for carrier hosts and intrinsic incubation in hosts. Analysis of the model reveals the following novel results. We show theoretically and numerically that vector feeding preference for carrier hosts plays an important role for the existence of both the endemic equilibria and backward bifurcation when the basic reproduction number R_0 is less than one. Moreover, by increasing the vector feeding preference value, backward bifurcation is eliminated and endemic equilibria for hosts and vectors are diminished.

Therefore, the vector protects itself and this benefits the host. As an example of these phenomena, we present a case of Andean Cutaneous Leishmaniasis (ACL) in Peru. We use parameter values from previous studies, primarily from Peru to introduce bifurcation diagrams and compute global sensitivity of R_0 in order to quantify and understand the effects of the important parameters of our model. Global sensitivity analysis via partial rank correlation coefficient (PRCC) shows that R_0 is highly sensitive to both sandflies feeding preference and mortality rate of sandflies.

Population heterogeneity and disease spread (Mathematical Epidemiology subgroup) / 474

Generation intervals in heterogeneous populations

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Generation intervals are an important and often-neglected component of the disease-transmission process. Mathematical models often assume exponentially distributed latent and infectious periods, but the interval between when a focal individual was infected and when they infect others (and the distribution of such intervals) can play a crucial role in parameterizing models and in making inferences and forecasts.

I will outline some issues involved in estimating generation intervals in populations with both spatial and individual-level heterogeneity, and discuss how these effect disease forecasts and estimates of disease parameters.

Population heterogeneity and disease spread (Mathematical Epidemiology subgroup) / 459

Modelling Human African Trypanosomiasis and the effects of domestic animals on transmission

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The Human African Trypanosomiasis (HAT) parasite, which causes African Sleeping Sickness, is transmitted by the tsetse fly as a vector. It has several possible hosts, including wild and domestic animals, who are not as negatively impacted by the disease as the human host. It has long been assumed that because domestic animals can be hosts for the parasite, that keeping domestic animals near human populations increases the spread of the disease. However, several parameters found in the literature, including the shorter lifespan of the male vector, and the female vector's preference for domestic animals, made us question this assumption.

We developed a differential equation compartmental model to examine whether increasing the domestic animal population can be used to deflect the infection from humans and reduce its impact. We have used numerical simulations and have examined the Basic Reproduction Number (R_0) for the model to quantify the effect of the domestic animal population on human infection. These analyses allow us to propose novel methods of controlling the impact of the disease on humans.

Positive equilibria of reaction network models / 114

Positive equilibria of weakly reversible power law kinetic systems with linear independent interactions

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In this talk, we present our results on power law kinetic systems whose kinetic order vectors (which we call “interactions”) are reactant-determined (i.e. reactions with the same reactant complex have identical kinetic order vectors) and are linear independent per linkage class. In particular, we focus on its subset called PL-TLK systems. Our main result states that any weakly reversible PL-TLK system has a complex balanced equilibrium. We can consider this result as a “Higher Deficiency Theorem” for such systems since in our previous work, we derived analogues of the Deficiency Zero and the Deficiency One Theorems for mass action kinetics (MAK) systems for them, thus covering the “Low Deficiency” case. On the other hand, our result can also be viewed as a “Weak Reversibility Theorem” (WRT) in the sense that the statement “any weakly reversible system with a kinetics from the given set has a positive equilibrium” holds. According to the work of Deng et al. and more recently of Boros, such a WRT holds for MAK systems. However, we show that a WRT does not hold for two proper MAK supersets: the set PL-NIK of non-inhibitory power law kinetics (i.e. all kinetic orders are non-negative) and the set PL-FSK of factor span surjective power law kinetics (i.e. different reactants imply different interactions).

Positive equilibria of reaction network models / 111

Rational steady state parametrizations for biochemical reaction systems

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Classical results give structural conditions under which the steady state set of a (bio)chemical reaction system has a monomial parametrization. This property has been studied extensively in the context of characterizing a mechanism's capacity for mono- and multi-stationarity. In this talk, we generalize the existing structural framework and derive sufficient conditions for guaranteeing that the steady states have a rational parametrization. Applications include the EnvZ-OmpR osmoregulation pathway and the Shuttled WNT signalling pathway.

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Multistationarity in biochemical reaction networks' models

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Multistationarity is defined as the existence of several positive equilibria of an ordinary differential equations model. Multistationarity is a required property of biological switches- reaction networks that govern important cellular functions, such as cell differentiation and cell death. This is the case, because biological switches are modelled by differential equations systems whose solutions can approach different stable equilibria depending on the initial conditions. Many differential equations models of reaction networks are known to be multistationary for particular parameter values. However, reaction networks' properties are robust in nature. Thus, for multistationarity to be robust, a reaction network has to be multistationary in some open region of parameter space. We will describe a computational procedure for screening dissipative differential equations models of reaction networks for the existence of multistationary regions. For a model of the double phosphorylation cycle, we have obtained simple parametric inequalities that identify multistationary regions in parameter space.

This is a joint work with C. Conradi (HTW-Berlin), E. Feliu and C. Wiuf (both from the University of Copenhagen).

Positive equilibria of reaction network models / 53

A deficiency zero theorem for a class of power law kinetic systems with independent decompositions

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In this paper, we study power law kinetics on chemical reaction networks with Independent decompositions, i.e. the network is the union of subnetworks whose reaction sets form a partition of the network's reaction set and the network's stoichiometric subspace is the direct sum of the stoichiometric subspaces of the subnetworks. Our main result is a Deficiency Zero Theorem when the subnetworks are weakly reversible and have linear independent reactant complexes (we denote the latter property as "zero reactant deficiency") and have kinetics with linear Independent kinetic order vectors (we denote this set of kinetics with "PL-RLK"). We elaborate the context of our result by presenting an overview of previous results on network decomposition (which we propose to call "Decomposition Theory") and a discussion of existing Deficiency Zero Theorems. To our knowledge, our result is the first Deficiency Zero Theorem which is valid for a class of kinetics which display non-reactant determined kinetic orders, i.e. there are reactant complexes whose branching reactions have differing kinetic order vectors (we call this set of kinetics "PL-NDK"). In previous work, we showed the occurrence of PL-NDK kinetics in numerous models of complex biochemical systems. We apply our results to characterize the positive equilibria of a power law approximation of R. Schmitz's model of the earth's carbon cycle in its pre-industrial state, which provided the original motivation for our study.

Poster Session - Board: 101 / 15

Extended logistic growth model for heterogeneous populations

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Cell proliferation is the most important cellular-level mechanism responsible for regulating cell population dynamics in living tissues. Modern experimental procedures show that the proliferation rates of individual cells can vary significantly within the same cell line. However, in the mathematical biology literature cell proliferation is typically modelled using a classical logistic equation with a constant proliferation rate, and this approach neglects variations in the proliferation rate. In this work we consider a discrete mathematical model of cell migration and cell proliferation, modulated by volume exclusion (crowding) effects, with variable rates of proliferation across the total population. We refer to this variability as heterogeneity. Constructing the continuum limit of the discrete model leads to a generalisation of the classical logistic growth model. Comparing numerical solutions of the model to averaged data from discrete simulations shows that the new model captures the key features of the discrete process. Applying the extended logistic model to simulate a proliferation assay using rates from recent experimental literature shows that neglecting the role of heterogeneity can, at times, lead to misleading results.

Poster Session - Board: 601 / 21

Optimal amplitude and frequency of breathing

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Physiological levels of oxygen and carbon dioxide in the blood are tightly regulated by varying the pattern of breathing, but this can be achieved with different combinations of amplitude and frequency. Why a specific combination of amplitude and frequency of breathing is observed remains a mystery. The aim of this study is to explore the hypothesis that the particular combination realised is optimal with respect to some objective function. Several objective functions have been suggested in the literature, such as the rate of work during inhalation, the average force exerted by the respiratory muscles, and the weighted sum of volumetric acceleration and work during inhalation; all of these objective functions provide physiologically acceptable minima under normal conditions. Resolving this issue requires optimal solutions of mathematical models that reflect more accurately the complex interaction between lung mechanics and gas exchange, but this in turn requires the development of new computational methodologies. To help achieve this goal, we constructed a simple mathematical model, consisting of two piecewise linear differential equations, that mimics gas exchange in the lungs. By using concepts from optimal control theory, we found the necessary conditions that minimise a given objective function subject to several constraints, such as satisfying the differential equations and maintaining one of the variables at a given average value. We could then solve the optimal control problem both analytically and numerically. Our method can be extended to models with higher dimensions.

Poster Session - Board: 604 / 224

A comparison of models of the glucose-insulin regulatory system for applications in circadian research

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Circadian clocks control 24-hour rhythms in the human body, including glucose and insulin dynamics. Glucose tolerance changes depending on the time of day and misalignment between environmental stimuli such as light and food and internal circadian clocks, e.g., as observed in shiftwork, is associated with metabolic disturbances and diabetes. The mechanisms of these are poorly understood. A number of mathematical models of circadian clocks and those of glucose-insulin dynamics have been developed. However, no model accounts for the interaction between the two systems. Here we examine and compare key existing models of glucose-insulin regulatory system with the aim to select the most appropriate model for incorporation of circadian rhythms.

A large number of mathematical models designed to study glucose-insulin dynamics have been developed over the past few decades and account for such key features as (i) ultradian oscillations, (ii) response to glucose infusion, and (iii) glucose homeostasis. The seminal model able to reproduce these oscillations was developed by Sturis *et al.* (1991) utilising a system of 6 ODEs. Since then, a number of other models have been adapted from this model, aiming to either reformulate the Sturis model—often as a system of DDEs—or to extend the model to allow other applications, for example in the Intravenous Glucose Tolerance Test. However, comparisons of the models with physiological experimental studies have been relatively limited in scope.

In this work, we compare the qualitative and quantitative predictions of the Sturis *et al.* (1991), Tolić *et al.* (2000), and Li *et al.* (2006) models and two other models with experimental results, under constant glucose infusion. We show the different parameter ranges in which the models display sustained ultradian oscillations and how this corresponds to the expected behaviour in published physiological studies. We also test the mean values, amplitudes, and frequencies of the simulated glucose and insulin concentrations against experimental studies. This sophisticated comparison of the models allows us to select the most appropriate model to incorporate circadian rhythms.

Poster Session - Board: 201 / 17

Models for the spread of *Wolbachia* in mosquito populations

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The vector-borne Dengue fever poses a major health issue in tropic environments, which includes areas such as far-north Queensland. Historically, attempts at curtailing the spread of dengue have focused on controlling the size and spread of mosquito populations that carry the virus. Several factors make this an astronomically difficult task to accomplish on any reasonable scale, however, and so more novel methods of suppressing dengue outbreaks are being explored. One such method is the introduction of bacteria called *Wolbachia* into mosquito populations, which prevents mosquitoes from passing on viruses to humans. A *Wolbachia* invasion has strong potential to completely saturate mosquito populations due to a mechanism called cytoplasmic incompatibility. The mathematical modelling problem here becomes twofold-first, the task of inferring the position of mosquito populations, and then the modelling of *Wolbachia* spreading through these populations. Here, we will be discussing the effects and mechanisms of *Wolbachia* in more detail, including the phenomenon of cytoplasmic incompatibility. Next, recent developments in modelling mosquito populations such as the use of semi agent-based models will be outlined, within the context of predicting the spread of *Wolbachia*.

Poster Session - Board: 204 / 153

A model for epidemic dynamics in a community with visitor sub-population

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With a five dimensional system of ordinary differential equations based on the SIR model, we consider the dynamics of epidemics in a community which consists of residents and visitors/tourists over a short period of time. The total population size of the community is taken to be constant, ignoring its change due to any birth and death in the period under consideration. Also, the resident and visitor populations are respectively constant. We assume that every immigrating visitor is susceptible and is likely to be infected during their stay in the community. Furthermore, infected visitors can carry on their activities normally during their stay in the community thus still appearing like susceptible visitors. From the analysis of the model, we obtained a threshold expected value of duration per visitor which determines whether an epidemic persists in the community or not. More so, the basic reproduction numbers with respect to the entire community as well as the resident and visitor populations are obtained and they can help us to formulate important public health policies in order to contain epidemics in the community.

Poster Session - Board: 609 / 378

A computational simulation of vascular deformation when subject to internally and externally applied forces

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The walls of our blood vessels are under a constant mechanical load, introduced by the blood pulsating through our vessels. Recent years have seen a substantial increase in the understanding of the interplay between the dynamics of blood flow (haemodynamics) and vessel (vascular) morphology. Alterations in the homeostatic distribution of mechanical forces exerted by blood on the vessel wall is correlated with various cardiovascular diseases, including atherosclerosis and aneurysm development and rupture. Furthermore, alterations in the haemodynamic distribution have a notable effect on vascular development and remodelling. Experimental analysis of the effects of blood flow on the local vasculature is invasive and extremely difficult to measure in real time. As such, the development of computational models to analyse the relationship between the local haemodynamics and the surrounding vasculature is invaluable.

In this project we will develop a computational model to study how vessels deform when subject to internally and externally applied forces. Using the open source multicellular modelling software package, Chaste, we will employ a discretised approach to simulate long time scale vascular wall deformation. A Voronoi tessellation-based model will be used to model vessel walls. This discretised model will enable us to examine how blood vessels deform when subject to internal and external forces, thus laying the foundations for future research examining vascular deformation due to haemodynamic pressure.

Poster Session - Board: 106 / 82

Differential priming and tolerance of monocytes challenged with external stimuli

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Cellular adaptation to varying signal strengths has been observed in the innate immune cells responses to external and internal challenges. Monocytes persistently challenged with low levels of external stimulants, can be skewed into a low-grade 'primed' state, while persistent challenges with high levels of external stimulants will skew them into a 'tolerant' state. Based on experimental and modelling studies, we have identified a generic network motif, composed of mutually competitive signals, as a potential principle for bistable and/or intermediate priming and tolerance responses. We use analytical and numerical techniques to identify the detailed mechanisms for the activation magnitude, duration, and potential transition between priming to tolerant states.

Poster Session - Board: 705 / 222

A multi-layered screening model for computational identification of leaf colour-related genes in rice plant

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Rice field art is a large-scale art form in which people design rice fields using various kinds of ornamental rice plants with different leaf colours. Leaf colour-related genes play an important role in the

study of chlorophyll biosynthesis, chloroplast structure and function, and anthocyanin biosynthesis. We performed whole-genome resequencing and transcriptomic analysis of regulatory patterns and genetic diversity among different rice cultivars to discover new genetic mechanisms that promote enhanced levels of various leaf colours. We re-sequenced the genomes of 10 rice leaf-colour varieties to an average depth of $40\times$ depth and $>95\%$ coverage and performed 30 RNA-seq experiments using the 10 rice varieties sampled at three developmental stages. The sequencing results yielded a total of $1,814 \times 10^6$ reads and identified an average of 713,114 SNPs per rice variety. Based on our analysis of the DNA variation and gene expression, we selected 47 candidate genes. We used an integrated analysis of the whole-genome resequencing data and the RNA-seq data to divide the candidate genes into two groups: genes related to macronutrient (i.e., magnesium and sulfur) transport and genes related to flavonoid pathways including anthocyanidin biosynthesis. We verified the candidate genes with quantitative RT-PCR using transgenic T-DNA insertion mutants. Our study demonstrates the potential of integrated screening methods combined with genetic-variation and transcriptomic data to isolate genes involved in complex biosynthetic networks and pathways.

Poster Session - Board: 501 / 8

Geometric analysis of synchronization in neuronal networks with global inhibition and coupling delays

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We study synaptically coupled neuronal networks to identify the role of coupling delays in network's synchronized behaviours. We consider a network of excitable, relaxation oscillator neurons where two distinct populations, one excitatory and one inhibitory, are coupled and interact with each other. The excitatory population is uncoupled, while the inhibitory population is tightly coupled. A geometric singular perturbation analysis yields existence and stability conditions for synchronization states under different firing patterns between the two populations, along with formulas for the periods of such synchronous solutions. Our results demonstrate that the presence of coupling delays in the network promotes synchronization. Numerical simulations are conducted to supplement and validate analytical results. We show the results carry over to a model for spindle sleep rhythms in thalamocortical networks, one of the biological systems which motivated our study. The analysis helps to explain how coupling delays in either excitatory or inhibitory synapses contribute to producing synchronized rhythms.

Poster Session - Board: 706 / 352

Model-based assessment of gene drive strategies to control pest populations in agricultural systems

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Agricultural systems throughout the world are threatened by a variety of pest species, including insects, pathogens and weeds. Conventional control methods often have limited success, notably in the case of pesticide use due to the ubiquitous development of resistance. Novel control approaches are therefore needed to improve management of these pest populations. Gene drive strategies, based on the use of genetic constructs with biased inheritance to drive traits into target populations, offer promising avenues for the development of such control methods, facilitated by the advent of

CRISPR-Cas molecular tools. Implementation of such strategies in agrosystems, with actively managed populations and strict socioeconomic constraints, offers a specific set of opportunities and challenges. Here we present a newly developed modelling framework design to study the outcome of these genetic control strategies in a variety of agricultural systems. This framework is built as a modular toolset that can simulate a wide range of scenarios, including a diversity of pest species, in a biologically and ecologically detailed fashion. We detail here the ability of this modelling tool to take into account specific aspects of the life history, ecology and genetics of the target organism. We introduce results demonstrating how genetic strategies can be used to control pesticide resistance. Finally, we discuss the future avenues of research offered by this theoretical framework, notably in terms of optimising implementation and deployment of genetic strategies in specific agrosystems, as well as investigating potential approaches for spatial and temporal containment of the associated genetic constructs.

Poster Session - Board: 802 / 127

Bond graph modelling of the cardiac action potential

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Bond graphs are an energy-based framework for modelling physical systems while adhering to thermodynamic and physical constraints, and they have recently been extended and applied to biochemical and electrophysiological systems. Here we describe a bond graph model of the cardiac action potential and use it to explore the issue of drift in mathematical models of electrophysiology, which is a cause of inaccuracy. Previous studies have linked drift to stimulus currents that violate conservation laws, but those analyses were restricted to individual models and relied upon the manual identification of conservation laws. Due to their adherence to conservation principles, bond graphs are well-suited for studying conservation laws under a more general framework. Using our bond graph approach, we found that the conservation law derived in previous studies is an example of a ‘conserved moiety’ within the bond graph modelling and metabolic analysis frameworks. Conserved moieties explain the occurrence of drift for a general class of models, demonstrating that bond graphs can provide a systematic approach that can be used to identify hidden conservation laws and check for the presence of drift.

Poster Session - Board: 803 / 240

Distinguishing cell shoving mechanisms

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Motivated by *in vitro* time-lapse images of ovarian cancer spheroids inducing mesothelial cell clearance, the traditional agent-based model of cell migration, based on simple volume exclusion, was extended to include the possibility that a cell seeking to move into an occupied location may push the resident cell, and any cells neighbouring it, out of the way to occupy that location. In traditional discrete models of motile cells with volume exclusion such a move would be aborted. We introduce a new shoving mechanism which allows cells to choose the direction to shove cells that expends the least amount of shoving effort (to account for the likely resistance of cells to being pushed). We call

this motility rule ‘smart shoving’. We examine whether agent-based simulations of different shoving mechanisms can be distinguished on the basis of single realisations and averages over many realisations. We emphasise the difficulty in distinguishing cell mechanisms from cellular automata simulations based on snap-shots of cell distributions, site-occupancy averages and the evolution of the number of cells of each species averaged over many realisations. This difficulty suggests the need for higher resolution cell tracking.

Poster Session - Board: 805 / 313

Adaptive life-history and eigenfunctions in structured population models

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Life-histories in organisms faced with various selection pressures such as heterogeneity, intra- and inter-specific competitions, and variable environment. Ecologists have thought that evolution maximizes different objects from each pressure. For example, in the absence of the competitions, conventional Darwinism asserts that the adaptive life history maximizes the population growth. On the other hand, the presence of competitions is thought to evolves un-invadable life strategy from any other strategies such as maximizing the carrying capacity that r/K -selection theory asserts. Difference of each habitat, thus, yields different objective function and diversity of life-histories from precocity to altricity.

However, there is ambiguity involved in necessity for different objective function in each habitat. It is difficult to define the threshold changing from population growth rate to carrying capacity, as objective function. This difficulty fades r/K -selection theory and makes ambiguity in categorization of life history evolution. On the other hand, several indices which the fittest species have are suggested (ESS etc.), and these have a common point that the fittest species or genetic group occupy their habitat. If an objective function addresses the common point without presence and absence of competitions, and if it evolves all traits that are precocity, altricity, and so on in life history, evolution of life-history can be systematized by maximizing (or minimizing) a unique objective function.

In this presentation, I would like to propose that the adjoint eigenfunction providing reproductive value in a structure population model is a candidate of the unique objective function.

Poster Session - Board: 810 / 508

Hybrid agent-based library

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The Hybrid Agent-based Library (HAL) is a Java Library made of simple, efficient, generic components which can be used to model complex spatial systems. HAL's components can broadly be classified into: on and off lattice agent containers, finite difference diffusion fields, a GUI building system, and additional tools and utilities for computation and collecting data. These components were designed to operate independently, but are standardized to make them easy to interface with one another.

HAL is a useful asset for researchers who wish to build efficient 2D and 3D hybrid models in Java, while not starting entirely from scratch. It is available on GitHub at <https://github.com/torococo/HAL> under the MIT License. HAL requires at least Java 8 or later to run, and the java jdk version 1.8 or later to compile the source code.

The spatial components in HAL all use a consistent indexing scheme. Setting values in a diffusible field, for example, is syntactically similar to setting visualization pixel values, or finding the agents that occupy a position. The consistent syntax helps substantially with HAL's learning curve. It also helps with understanding the source code of models that use components that the reader is not familiar with.

There are several pre-existing general hybrid agent-based modelling frameworks, the most popular being Chaste, Repast, Mason, and Netlogo. Each of these facilitates modelling under a different centralized control structure: In Chaste centralized control done by a Simulator object, in Repast this component is called an Engine, in Mason it is called the Schedule object, and in Netlogo it is called the Go loop.

HAL shares many characteristics with these frameworks, but primarily differentiates itself with its simplicity and decentralized design. There is no controller or scheduler, so the modeler designs the logical flow and the scheduling of interactions between components of the model explicitly. This allows the modeller to define the execution of the model using simple programming constructs such as "for loops", and sheds the difficulty of learning to manipulate a more complex control architecture.

Poster Session - Board: 701 / 29

Putting your money where your mouth is: the economics of stomatal development

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The placement of stomata on the leaf surface is regulated by a number of things: coordinated asymmetric cellular division, genetic regulation, and distribution of extracellular signalling molecules.

It has been noted that the number of stomata per non-stomatal epidermal cell can vary between plants which have the same spatial distribution of stomata, which suggests that in some circumstances one method of maintaining stomatal placement (increased cell division, increased cell expansion, increased recruitment of cells to the stomatal fate) may be optimal over another.

Perhaps the reason for this difference in stomatal placement regulation is due to difference in the energetic costs to the plant of each of these methods. Using a combination of experimental and mathematical biology, the relationship between energetic cost and stomatal placement in the model organism *Arabidopsis thaliana* is being investigated.

Poster Session - Board: 704 / 186

Analysis of effects of vector preference on the transmission of insect-borne plant diseases

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Recent studies have shown that pathogens can alter the behaviour of hosts or vectors to improve their transmission power. This happens not only in animal pathosystems but in plant pathosystems. While animal pathogens can alter the behaviour of both hosts and vectors in ways that increase frequency of host-host or host-vector encounters, in plant pathosystems the host does not have mobility, so the potential for behavioural manipulation is restricted to just vector mobile component in these systems [1].

Motivated by [2], we investigate how this manipulation affects transmission of specific insect-borne plant diseases. To do so, we use the compartmental model of vector preference in which the probability of which vectors settle on individual host plants. Then we demonstrate that interactions between host and vector infection status, the effect of a vector preference and difference of the effect between animal- and plant systems. together with any evolutionary implications.

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Poster Session - Board: 308 / 400

Phenotypic and genotypic competition models on lattice space

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Barreto *et al.* (2017) studied the rock-paper-scissors games (or cyclic competition games) by the dynamics of phenotypic and genotypic frequencies corresponding to three morphs of lizards. In their model they show that both dynamics have equal internal equilibrium but the genotypic model has wider parameter range for its stability compared to the phenotypic model.

Here, first of all, we investigate phenotypic and genotypic competition models with two-species. Then we consider the Barreto *et al.* model with different genotypic correspondence to three phenotypes. Lastly computer simulations for these models are carried out on lattice space and the effects of spatial structure are discussed.

Poster Session - Board: 205 / 249

A mathematical model for the effect of domestic animals on the basic reproduction number of Human African Trypanosomiasis (Sleeping Sickness)

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The Human African Trypanosomiasis (HAT) parasite, which causes African Sleeping Sickness, is transmitted by the tsetse fly as a vector. It has several possible hosts, including humans and domestic

animals. Because domestic animals can be a host for the parasite, it has long been assumed that keeping domestic animals near human populations increases the spread of the disease. However, several parameters found in the literature, including the shorter lifespan of the male vector and the female vector's preference for domestic animals, made us question this assumption.

We have developed a differential equation compartmental model to examine whether increasing the domestic animal population can be used to deflect the infection from humans and reduce its impact. This 9-dimensional system of nonlinear ordinary differential equations includes tsetse flies in their various stages of maturity, which is more than most previous models have done. We used the Next Generation Matrix method to obtain an expression for R_0 , the basic reproduction number, based on the other parameters in the model.

Our study indicates that strategies that were not previously considered, such as vaccinating domestic animals, may reduce the impact of the disease on humans even better than vaccinating humans.

Poster Session - Board: 112 / 353

A model of calcium dynamics in anatomically accurate parotid acinar cells

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We constructed an anatomically-accurate three-dimensional model of salivary fluid secretion from a cluster of parotid gland acinar cells.

Parotid acinar cells are responsible for the secretion of saliva. Olfactory and gustatory stimuli provoke the release of agonists that bind to the basal membranes of the acinar cells. This triggers a cascade of events that results in the production of IP₃, which, in turn, releases calcium ions from intracellular compartments. Upon release of calcium, chloride channels are activated, leading to chloride ions flowing out of the cell, and water following by osmosis.

We have shown previously that the complex spatial structure of the acinus and the spatial heterogeneities within each acinar cell imposes severe constraints on the possible mechanisms that could explain the saliva secretion process.

We will discuss how could we simplify the models that are able to replicate the physiological observations under such constraints.

Poster Session - Board: 607 / 253

Dynamical patterns in brain parenchyma : modelling approach and Issues

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Recent advances in understanding of complex interactions between the processes that maintain and control the physiological state of brain parenchyma open new possibilities and deliver new challenges for modelling studies on topic. Now it is clear that any significant deviation from normal conditions as well as natural alternations of activity of cortical neurons (say, during sleep-wake cycle) are accompanied by measurable changes of physiological parameters, like extracellular ionic

concentrations, astrocytic calcium signalling, or vascular tone of adjacent blood vessels. The interaction pathways within the so called neural-glial-vascular unit not only drive the local responses of the cells, but form the spatially extended networks at different functional layers.

Being normally on the sidelines, these physiological mechanisms become dominant during the extreme physiological behaviours of the brain cortex, such as cortical spreading depression, migraine waves, or spreading depolarization events with stroke or injuries. There is a clear room and need for relevant modelling studies aimed to better understanding of how all this activity is orchestrated. However, this task is very challenging due to the extreme complexity and heterogeneity of system under study.

The presented study addresses the selected aspects of above problem. Being focused on dynamical patterns, we still keep the balance between the physiological details and dynamically tractable generalized modelling. First, we discuss the dynamical consequences of inclusion of extracellular potassium concentration as a state variable in neuron models. Specifically, this additional variable provide both the self-sustained depolarization, and the additional pathway for cell-to-cell signalling which is also known as “volume connection”. Second, we extend this potassium driven model to the mathematical model of cortical spreading depression which counts the effects of neurovascular coupling and cerebral blood flow redistribution. Our most notable finding here is that the combination of vascular-mediated spatial coupling with local regulatory mechanisms results in the formation of stationary Turing-like patterns during a course of spreading depolarization.

Third, we describe a way to incorporate in model the recently revealed details of astrocyte morphology and functions. This approach includes the algorithms for the creation and computational treatment of spatial patterns resembling the real astrocyte networks.

In conclusion, as an outlook, we discuss how the dynamical redistribution of extra- and inter-cellular volumes could affect the reported dynamics, as well as formulate the issues related to adequate modelling of vascular-mediated spatial interaction.

Poster Session - Board: 206 / 271

Multi-scale and multi-compartment modelling provides insight to vaccination dynamics in Tuberculosis

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Tuberculosis (TB) is one of the top 10 causes of death worldwide, and the WHO's EndTB strategy requires developing an effective vaccine. The H56 vaccine is a candidate currently in phase I/IIa trials as a boost to Bacillus Calmette-Guérin (BCG, the TB vaccine that is currently used in most countries world-wide). We build a multi-compartment, hybrid multi-scale model to 1) improve our understanding of immune response to H56 and 2) predict the role of T cells in preventing TB after vaccination.

First, we develop a two-compartment model of 31 non-linear ordinary differential equations (ODEs) that describe T-cell priming, proliferation, and differentiation in lymph nodes and blood. These ODEs allow us to track T cell response following vaccination. We calibrate our ODE model separately to human clinical trial data and non-human primate (NHP) experimental data to display differences

in each species response to H56. Next, we couple our curated agent based model of granuloma formation in the lung, GranSim, to our blood and lymph node compartments to capture the host immune response to infection with *Mycobacterium tuberculosis*. This creation of a multi-scale and multi-compartment model allows us to represent a pseudo-whole-body response to both vaccination and infection. We use this whole-body model in the form of “virtual clinical trials” to retrospectively study the human and NHP datasets. In particular, we predict the role of T cells (induced through vaccination) throughout the course of infection in blood, lymph node, and lung granulomas. We use uncertainty and sensitivity analysis to compare and contrast immune response to vaccination and infection in NHPs and humans. We conjecture that vaccine dose may be critically important when evaluating H56 efficacy against *Mycobacterium tuberculosis* infection.

Poster Session - Board: 801 / 39

Mathematical modelling of bacterial growth at different scales: numerical simulations and laboratory experiments

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Biofilms are sessile communities of bacteria housed in a self-produced adhesive matrix consisting of extracellular polymeric substances (EPS), including polysaccharides, proteins, lipids, and DNA. [1]. Biofilm provokes chronic bacterial infection, infection on medical devices, deterioration of water quality, and the contamination of food [2]. On the other hand, biofilm can be used for wastewater treatment and bioenergy production [3]. In microbial enhanced oil recovery (MEOR), one of the strategies is selective plugging, where bacteria are used to form biofilm in the high permeable zones to diverge the water flow and extract the oil located in the low permeable zones [4]. Therefore, it is necessary to build mathematical models that better describe the biofilm mechanisms. One of the motivations to derive upscaled models is to describe the averaged behaviour of the system in an accurate manner with relatively low computational effort compared to fully detailed calculations starting at the microscale [5]. In the laboratory, biofilm is grown in a T-shape micro-channel. We built a mathematical model including water flux inside the biofilm and different biofilm components (EPS, water, active bacteria, and dead bacteria). Using the best estimate of physical parameters from the existing experiments, we perform numerical simulations. The stress coefficient is selected to match the experimental results. A sensitivity analysis is performed to identify the critical model parameters. A reduction of the biofilm coverage area as the water flux velocity increases is observed. Homogenization techniques are applied in a strip and a tube geometry. Numerical simulations are performed to compare both upscaled mathematical models. In the macro-scale laboratory experiments, biofilm is grown in cylindrical cores. Permeability changes over time at different flow rates and nutrient concentrations are studied. Numerical simulations are performed to compare with the experimental results.

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Poster Session - Board: 804 / 306

Construction of quasi-potential landscapes using the Sum-of-Squares optimisation

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The construction of effective and informative landscapes for stochastic dynamical systems has proven a long-standing and complex problem, including for biological systems. Such landscapes may refer to a true energy function for cases such as protein folding or to a phenomenological metaphor in the case of Waddington's epigenetic landscape. In many situations, constructing a landscape comes down to obtaining the quasi-potential, a scalar function that quantifies the likelihood of reaching each point in the state-space.

In this work we provide a novel method for constructing such landscapes using a tool from control theory: the Sum-of-Squares method for generating Lyapunov functions. Applicable to any system described by polynomials, this method provides an analytical polynomial expression for the potential landscape, in which the coefficients of the polynomial are obtained via a convex optimisation. The resulting landscapes are based upon a decomposition of the vector-field of the original system, such that the inner product of the gradient of the potential and the remaining dynamics is everywhere negative. By satisfying this condition, our derived landscapes provide both upper and lower bounds on the true quasi-potential; these bounds becoming tight if the decomposition is orthogonal. The method is implemented in the programming language Julia, and is demonstrated to correctly compute the quasi-potential for high-dimensional linear systems and also for a number of nonlinear examples. For a multi-stable stochastic system analogous to a developing stem cell, we use the computed potential to evaluate bounds on the relative likelihood of reaching fixed points equivalent to each of the differentiated phenotypes.

Poster Session - Board: 255 / 320

Dynamic model predicting overweight and obesity in Korean adolescents

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Obesity is the result of caloric imbalance and is mediated by genetic, behavioural, and environmental factors. Healthy lifestyle habits, including healthy eating and physical activity, can lower the risk of becoming obese and developing related diseases. The prevalence of obesity among Korean adolescents aged 13 to 18 years increased from 13.65% in 2007 to 19.3% in 2016 for boys.

We analyze trends in adolescents obesity for 6 years and estimate of adolescents obesity. We adopt the well-known SIR model structure for infectious diseases. A differential equation system predicted adolescents' obesity prevalence trends. The model considers both social environment and obesogenic environment influences on weight gain, incorporates other known parameters affecting obesity trends.

The dynamic model predicts that obesity prevalence will plateau independent of current prevention strategies. The proportion of overweight is lower in middle school than in high school, but obesity is higher in high school. The adolescents prevalence of overweight and obesity for boys will plateau by about 2025 at 6% and 27% respectively.

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Poster Session - Board: 111 / 339

Modelling saliva secretion

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We constructed a dynamical model of a salivary gland acinar cell with the objective of investigating the role of two plasma membrane (PM) anion exchangers, the Ae2 (Slc4a2) and Ae4 (Slc4a9), in primary fluid secretion. Transepithelial chloride (Cl^-) movement drives water transport in salivary gland acinar cells. Basolateral PM mechanisms accumulate Cl^- to levels well above its electrochemical equilibrium. Following an increase in the intracellular concentration of calcium (Ca^{2+}), a Cl^- efflux through apical Ca^{2+} -dependent Cl^- channels (TMEM16a) generates a transepithelial osmotic gradient. Water follows this gradient by osmosis. Cl^- uptake via basolateral co-transporters (Nkcc1), provides the major force for generating fluid secretion in acinar cells. Despite this, Nkcc1 knockout experiments saw an approximate 70% decrease in gland salivary rate. The residual secretion is bicarbonate (HCO_3^-) dependent and involves two sodium/proton (Nhe1) paired $\text{Cl}^-/\text{HCO}_3^-$ anion exchangers, the Ae2 and the Ae4. Experiments revealed that Ae4 knockout mice displayed a decreased gland fluid secretion ($\sim 30\%$ of the control fluid flow rate) whilst Ae2 knockout mice gland salivation remained intact. The reason behind the results remains a controversial topic. Our model's results reproduce and support the experimental observations. More importantly, they suggest that the Ae4 cotransport of monovalent cations is likely to be important in establishing the osmotic gradient necessary for optimal transepithelial fluid movement.

Poster Session - Board: 602 / 43

Mathematical dynamics of clustered ventilation defects in asthmatics

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Asthma is a chronic lung disease of reversible airway constriction. Imaging experiments show that during an asthma attack, the asthmatic's lung exhibits what is known as clustered ventilation defects, which is the hallmark trait of asthma. This phenomenon is when there are some regions of the lung where the airways are closed, and some regions where they are open. These clusters vary from event to event, even in the same patient, and thus it is believed that the causes are dynamic rather than structural. We want to understand the dynamic mechanisms behind the physiological implications. Different mechanisms leading to spatial clustering have been suggested; we are interested in assessing the physiological viability of some of these models, particularly with how each model exhibits this spatial clustering. During this talk, we will go over these models and how they have shown themselves to be different in the dynamics analysis.

Poster Session - Board: 605 / 234

Integrative compartmental model of carnitine and its derivatives

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Carnitine is a fundamental compound for humans. Mainly introduced via nutrition, but also synthesized in the body, this metabolite allows the transport of long-chain fatty acids in the mitochondria, where they can undergo β -oxidation. Lately, the attention on carnitine and acyl-carnitine, carnitine derivatives, has increased since it has been proposed that insulin resistance may be linked to incomplete fatty acid β -oxidation and the subsequent increase in acyl-carnitine species in different tissues.

Mathematical modelling can give us a quantitative understanding of specific rates in the carnitine metabolism, e.g. synthesis of carnitine derivatives. Therefore we contribute to the research on carnitine by building a compartmental model for carnitine and its derivatives. This model integrates knowledge about carnitine uptake and synthesis, carnitine distribution and expulsion, and carnitine role in the transport of long-chain fatty acids, therefore covering all the carnitine occurrences in the body. Additionally, the simultaneous comprehension of carnitine and its derivatives enables the model to highlight the role of carnitine concentration as a bottleneck in the transport of the long-chain fatty acids into the mitochondria.

Our model utilizes metabolome datasets publically available in the literature for validation.

Poster Session - Board: 606 / 243

Control of the cardiorespiratory system: challenges and opportunities

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Maintaining physiological levels of oxygen (O_2) and carbon dioxide (CO_2) in the blood is crucial for survival and is achieved by sophisticated neural control mechanisms affecting both the breathing pattern and heart rate. Neural activity, originated in the brainstem, drives the respiratory muscles, providing air flow into and out of the lungs where gas exchange takes place and also affects heart rate and blood flow. Chemoreceptors that sense the levels of O_2 and CO_2 in the blood, mechanical stretch receptors within the lungs and blood pressure sensors provide feedback signals to the brainstem networks which then regulate the breathing pattern and heart rate appropriately. Understanding how the neural system responds to all the feedback signals it receives is still lacking. I will outline the challenges we face from a modelling perspective and the different approaches we take in our attempt to resolve them.

Poster Session - Board: 806 / 382

Agent-based modelling of higher order chemical reactions using Smoluchowski kinetics

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Chemical reactions are traditionally modelled using deterministic methods such as ordinary differential equations. In biology, we also consider the effect of diffusion upon a reactive system. For small biological systems, it is necessary to use stochastic models. In this talk, we choose to use an agent-based model commonly known as Smoluchowski kinetics.

In the Smoluchowski model, two molecules diffuse in space, and react when they are within a critical separation distance (Smoluchowski radius). This radius is at a rate proportional to the reaction rate constant. Over the last 100 years, the model has been extended to incorporate reversible reactions by introducing a second separation distance.

A common problem with Smoluchowski kinetics is when modelling rapid enzyme reactions, where the assumptions used to model Smoluchowski kinetics break down. Using differential equations, these rapid interactions can be easily analysed using a pseudo steady state approximation which effectively results in non-linear reactions. Other models have utilised multiple timescales to model what is called fast-slow reaction kinetics.

In this talk, we theorise that a way to bypass the fast-slow reaction kinetics problem is to extend the Smoluchowski model to reversible trimolecular reactions. We develop these kinetics and apply them to the canonical Wnt signalling pathway. We model this pathway using traditional Smoluchowski kinetics, and show how the aforementioned issues come into effect. We then compare this to our trimolecular model and show how the issues disappear.

Poster Session - Board: 113 / 358

The interplay between feedback and buffering in cellular homeostasis

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Negative feedback and buffering, the use of reservoirs of molecules to maintain concentrations of key molecular species, are the primary known mechanisms for robust homeostatic regulation. However, the fundamental principles behind their combined effect have not been elucidated. Here, I will present our recent research on the interplay between buffering and negative feedback in the context of cellular homeostasis. This research shows that negative feedback counteracts slow-changing disturbances, whereas buffering counteracts fast-changing disturbances. Furthermore, feedback and buffering have limitations that create trade-offs for regulation: instability in the case of feedback and molecular noise in the case of buffering. However, because buffering stabilizes feedback and feedback attenuates noise from slower-acting buffering, their combined effect on homeostasis can be synergistic. These effects are consistent with experimental observations of both ATP homeostasis and pH regulation *in vivo*. The methodology is based on control theory and complexity-aware minimal modelling. The discussed principles are crucial for studying robustness and homeostasis in biology and biotechnology.

Poster Session - Board: 807 / 383

An approach and tools for research reproducibility across computational biology

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Reproducibility of results is a key part of the scientific method; in general, scientific communication aims to describe a result in enough detail that readers and reviewers are able to contextualise the result within their own knowledge, and to reproduce it themselves given the appropriate skills and resources. In the field of computational biology, readers and reviewers face special challenges to contextualise and reproduce results, because of the size of datasets analysed, and the increasing complexity of the computational methods used. To meet these challenges, we present an approach that uses software engineering tools to produce complete ‘reference computation environments’, containing all software and configuration necessary to reproduce a computational result. Existing tools to reproduce results are limited to a single technology or programming language; our approach is the first to use a single specification to produce the same environment on a desktop computer, in a cloud computing service, or in a managed computing facility. Using these tools, authors can ensure their published results are easily reproducible by readers and reviewers, and are robust to future changes in software and hardware.

The drive for reproducibility in the computational sciences has provoked discussion and effort across a broad range of perspectives: technological, legislative/policy-making, education, and publishing. Nature Biotechnology has recently implemented standards for reproducibility [1] in response to increasing complexity of methods and data requirements in computational biology. Discussion on these topics is not new [2,3,4], but the need to adopt standards for reproducibility of claims made based on computational results is now clear to researchers, publishers and policymakers. Many technologies exist to support and promote reproduction of results: this journal and others have discussed containerisation tools like Docker [5], literate programming approaches such as Sweave [6], knitr [7], iPython [8] or cloud environments like Amazon Web Services [9]. But these technologies are tied to specific programming languages (e.g. Sweave/knitr to R; iPython to Python) or to platforms (e.g. Docker for 64-bit Linux environments only). No single approach to date is able to span the broad range of technologies and platforms represented in computational biology and biotechnology.

To enable reproducibility across computational biology, we demonstrate for the first time an approach and a set of tools that is suitable for all computational work, and not tied to a particular programming language or platform. Our approach extends our previous work in this area [10] to produce ‘reference environments’ for reproducing results that can be deployed across platforms and can use any and all of the replication tools described above. We achieve this by adopting innovative open-source tools from software engineering [13,14], and we are now involved in the community contributing to the development of these tools, and acting as advocates for scientific computing within that community. We present published examples from a series of papers across research groups in different areas of computational and systems biology, spanning the major languages and technologies in the field (Python/R/MATLAB/Fortran/C/Java). We also include examples reproducing studies in network analysis by Feizi *et al.* [11] and Barzel *et al.* [12], results which have been recently commented upon in this journal [1]. We also present results from another study demonstrating that different output values can be produced from the same data and code given different versions of the MATLAB software used by the Feizi and Barabasi codebases. Since very few reviewers and readers will run the same code using multiple software versions, this could be interpreted as inability to reproduce the published work, underlining the need for a reference environment as produced by our approach. Our approach produces a transparent and flexible process for replication and recomputation of results, but ultimately its most valuable aspect is the decoupling of methods in computational biology from their implementation. Separating the ‘how’ (method) of a publication from the ‘where’ (implementation) promotes genuinely open science and benefits the scientific community as a whole.

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Poster Session - Board: 212 / 331

An optimal impulse control problem in anti-cancer therapeutic strategies

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We present an optimal impulse control problem related to anti-cancer therapeutics. Our model takes into account both the instantaneous toxicities of the treatments and the adverse effects of targeted and non-targeted antineoplastic therapies.

Poster Session - Board: 114 / 386

Error-correcting DNA barcodes for high-throughput sequencing

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Many large-scale high-throughput experiments use DNA barcodes—short DNA sequences prepended to DNA libraries—for identification of individuals in pooled biomolecule populations. However, DNA synthesis and sequencing errors confound the correct interpretation of observed barcodes and can lead to significant data loss or spurious results. Widely-used error-correcting codes borrowed from computer science (e.g., Hamming and Levenshtein codes) do not properly account for insertions and deletions in DNA barcodes, even though deletions are the most common type of synthesis error. We present and experimentally validate FREE (Filled/truncated Right End Edit) barcodes,

which correct substitution, insertion, and deletion errors, even when these errors alter the barcode length. FREE barcodes are designed with experimental considerations in mind, including balanced GC content, minimal homopolymer runs, and reduced internal hairpin propensity. We generate lists of barcodes with different lengths and error-correction levels that may be useful in diverse high-throughput applications, including $> 10^6$ single-error correcting 16-mers that strike a balance between decoding accuracy, barcode length, and library size. Moreover, concatenating two or more FREE codes into a single barcode increases the available barcode space combinatorially, generating lists with $> 10^{15}$ error-correcting barcodes. Our software for creating barcode libraries and decoding sequenced barcodes is efficient and designed to be user-friendly for the general biology community.

Poster Session - Board: 404 / 401

Fixation probabilities of mixed-strategies for bimatrix games in finite populations

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Stochastic evolutionary game dynamics in finite populations has recently been examined not only for symmetric games [1] but also for bimatrix games [2]. While in these studies the fixation probabilities of pure strategies are investigated, this study examines the evolutionary dynamics of two-player 2 by 2 bimatrix games with mixed-strategies in finite populations under weak selection. The game has two populations for row and column players. In the population consisting of row (column) players, two types of players, i.e., mutant and wild-type players, have different mixed-strategies which assign different weight to the two row (column) strategies. Each player's fecundity is determined by the average payoff obtained by interactions with all players in the opposite population. The process of death and birth of players is modelled by the frequency-dependent Moran process.

For this game, I derived the fixation probabilities that a pair of mixed-strategies by mutants in the row and column populations takes over the entire populations from a given initial state. Moreover, based on the probabilities, I discuss the stochastic stability of the pair of mixed-strategies played by wild-type players.

In addition, the fixation probabilities of mixed-strategies of mutant players when the selection is weak because of mixed-strategies played by mutant and wild-type players being very close in terms of a probability distribution over the set of possible strategies, which are the counterparts of Wild and Traulsen [3] in bimatrix games, are also discussed.

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Poster Session - Board: 808 / 415

Topological analysis of the three dimensional structure of antibody

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In silico prediction of the relationships between the protein structure and its physiological activity is an important research topic for drug design. Broad picture of my research is to construct a topological model to clarify the antibody-antigen recognition system, since immunotherapy is applied to wide range of severe diseases such as cancer [1].

To achieve the goal, we focus on a topological method called “Fatgraph models of proteins” [2]. Fatgraph models of proteins are topological two-manifold with boundary components (surface) which have one to one correspondence with three-dimensional protein structures listed on Protein Data Bank (PDB) [3] with only a few exceptions. The traits of each surface for each protein are described by the following invariants; Euler characteristics, number of boundary components, and genus. Fatgraph is also called ribbon graph and has already proven their utility in theoretical physics including string theory [4].

In this research, we constructed fatgraph models of antibodies and investigated the traits of antigen-binding fragments (Fab). Then, we topologically examined the transformations of the fatgraphs of the proteins due to the changes of protein sequences or existence of ligands.

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Poster Session - Board: 256 / 374

Mathematical modelling of cancer cell morphological and phenotypic plasticity in response to the extracellular matrix

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The occurrence of distant metastases greatly reduces or even removes the possibilities of curative treatment for cancer patients. The development of tools for predicting and diagnosing the onset of secondary tumours has long been a significant subject of cancer research effort. Moreover, it is widely known that while in some tissues cancer cells exhibit higher proliferation, in others they are more invasive so the best treatment strategy should be chosen accordingly.

A novel tissue engineering approach was created in our group in order to gain insight into the processes of cell growth, motility and invasion. Organ-specific scaffolds were seeded with highly invasive triple negative breast cancer cells. These tissue engineering constructs (TECs) were then cultured in vitro for 4 weeks and the resulting patterns of cell colonisation of extracellular matrix (ECM) were analysed.

One of the most noteworthy results of this experiment is the emergence of two alternative strategies of matrix colonisation depending on the origin and structure of the underlying ECM. In particular, we observed significant differences in cellular attachment efficiency, morphology, density and invasion of the breast cancer cells.

To gain a better understanding of cellular behaviours and validate the hypothesis that colonisation pattern strongly depends on the properties of ECM, we developed a corresponding mathematical

model of tumour growth in TECs. For these purposes, we used a lattice-based stochastic approach based on the energy formalism, where the concept of cell adhesion is considered the key mechanism of cell-cell and cell-ECM interactions. Our model reproduces the early stage of the experiment (the stage characterised by rapid colonisation of surface and subsurface matrix layers) showing a clear distinction in cell morphology and spatial distribution when varying the density of adhesion molecules expressed on the matrix.

Further, to expand the computational model and attribute the role of the underlying ECM to cell invasion and clustering inside the tissue, we ran a set of single-factor experiments, each designed to reveal the effect of a specific physical property of the matrix. Statistical analysis of the experimental data provides estimations of model parameters and complements the picture of cell-matrix interactions.

We believe that this data-driven approach will allow predicting phenotypical and morphological changes of cancer cells and the subsequent preferred mode of tissue colonisation, which is essential for the choice of appropriate treatment.

Poster Session - Board: 707 / 450

Modelling of a moving net observed in a plant endoplasmic reticulum

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An endoplasmic reticulum (ER) is a tubular organelle observed in cells of eukaryote including the plants and animals. Interacting with flow of actin cytoskeleton, the net-like pattern organized by ER in plant cells is continuously moving.

For the understanding of this system, we constructed a mathematical model based on a partial differential equation (PDE). By combining two spatially distributed structures, an arbitral periodic pattern by PDE and an actin mesh dependent perturbation, we successfully obtained the dynamics of the system.

In this model, it was found that the filamentous actin distribution was not necessarily needed and static perturbations were sufficient to move the pattern. Then the pattern periodicities were disturbed when the dynamics of system could be observed. Therefore, we inferred that, though it might seem paradoxical, the capacity to maintain the order and the symmetry of pattern generate the dynamics.

This theory is considered to explain one of the basic elements to generate a dynamic pattern, therefore, further discussions are needed to define the minimal conditions for giving the motility. We will comparative investigate the following points (1) pattern property effected by the perturbations and (2) distribution manners and types of perturbation. Then the periodicity and the motilities of pattern will be analyzed quantitatively.

Poster Session - Board: 310 / 454

Comparative physiological energetics of three commercial tuna species

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Interspecies comparisons of physiological energetics are possible only through the prism of a formal metabolic approach such as the Dynamic Energy Budget (DEB) theory which uniformly describes how individuals of different species acquire and utilise energy. We used the DEB theory to infer the energy budgets of three commercial tuna species (skipjack, Pacific bluefin, and Atlantic bluefin) throughout all stages of ontogenetic development—from an egg to an adult individual and its eggs. Energy budgets were inferred from scarce and disjointed data sets fed into a DEB-based mathematical model tailored for tuna fish until reaching a high goodness of fit and thus the reliable estimates of the model parameters.

The results show that life histories of all three species are strongly influenced by morphological and physiological adaptations which accelerate ontogeny during the larval stage, although the effect is more pronounced in bluefin than skipjack tuna. We identify that in energetic terms the accelerated ontogeny is a simultaneous improvement of energy acquisition (higher intake) and utilisation (higher expenditure) without changing the capacity of fish to build energy reserve as intake and expenditure increase in unison. High energy expenditure, an even higher intake by necessity, and a limited capacity to build energy reserve, make all three tuna species vulnerable to starvation, thereby theoretically underpinning the description of tuna fish as “energy speculators”. We furthermore find that energy allocation to reproduction maximises fecundity of all three tuna species, thus suggesting that the evolution of tuna favoured higher fecundity at the expense of growth.

Thinking beyond just physiological energetics (e.g., wild stock projections), we discuss why DEB-based models are a natural foundation for physiologically structured population dynamics wherein the environment influences the population growth rate via metabolism. We suggest several concrete modelling techniques which allow progress in this direction.

Poster Session - Board: 216 / 96

A multiscale PDE model of hepatitis C virus infection formulated to ODE model

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Direct-Acting antivirals (DAAs) target intracellular viral replication and have realized high effectiveness for hepatitis C virus (HCV) patients. Now, many kinds of DAA drugs have discovered and the HCV treatment is improving day by day. A popular strategy of HCV treatment is combination of double or triple DAA drugs with different action mechanisms. Mathematical model is used to analyze the dynamics of virus infection and effectiveness of antiviral drugs. For DAA treatment, multiscale model formulated by partial differential equations (PDE) describing both intercellular virus infection and intracellular virus RNA replication is used. However, in general, numerical computation of PDE often converge poorly and is time consuming. So it is somewhat hard to estimate parameters, and we should transform the PDE to easier form in advance of analyzing the model. In our study, we transformed the PDE model to ODE form without any assumption. Thus our ODE model and the previous PDE model are mathematically identical. By this transformation, the time required for numerical simulation is reduced greatly and we can apply some basic analysis methods for dynamical systems of ODEs to the multiscale model.

Poster Session - Board: 506 / 278

Influence of receptor recharge on the statistics of captured particles

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We consider a setup in which n particles are initially released into a domain and diffuse freely. Part of the boundary consists of absorbing “escape” regions, where the particles can escape the domain, and reflecting regions. The rest of boundary consists of “capture” regions (receptors), that can switch between being reflecting and absorbing. Specifically, after capturing a particle, the capture region becomes reflecting for an exponentially distributed amount of time (recharge time). We are interested in the distribution of the number of particles that are captured before they escape.

Our mathematical results are derived from considering our system in several ways: as a full spatial diffusion process with recharging traps on the boundary; as a continuous-time Markov process approximating the original system; and lastly as a system of ODEs in a mean-field approximation.

Considering the full spatial diffusion process, we prove that the total expected number of the captured particles has an upper-bound of the order of $(\log n)$. We then consider a few examples investigating the implications of this result, including a neural system in which recharge reduces the number of neurotransmitter bindings by several orders of magnitude.

Seeking additional understanding of this process over a wide range of parameter values, we then present a well-defined algorithm to approximate the full spatial diffusion process with a continuous-time Markov process in order to eliminate computationally expensive simulations. We highlight the conditions required for the approximation to yield similar quantitative results as the full spatial process. We then apply the approximation, and the associated mean-field model, to investigate time courses for the expected number and higher ordered statistics of captured particles. Specifically, we find that the number of expected captures as a function of time appears to grow linearly, before leveling off, and find an analytical expression for the duration of the linear growth. This result may be particularly helpful for understanding applications where multiple puffs of particles are inserted in the domain over a period of time (e.g. neuronal synapses), and can provide a bound on the time between puff events such that particles in different puffs no longer interact. We also find that the amount of variation observed in the total number of captured particles varies non-monotonically with the mean recharge time. Lastly, we combine these results together to predict stochastic properties of intracellular signals resulting from receptor activation.

Poster Session - Board: 608 / 375

Modelling and characterizing the folding patterns of the human brain

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The human brain consists of folds (gyri) and valleys (sulci) that vary dramatically in their size, extent, and shape across individuals. There is considerable debate among biologists as to how the folding patterns develop and if the folding patterns can be used to diagnose disease. In this presentation, I will discuss some of the mathematical and modelling approaches my research group is developing to study cortical fold formation, Turing patterns, topology, conformal mapping, and conformal invariants are some of the methods we are using to model and characterize the folding patterns of

the brain in development, health, and disease. By altering various model parameters, including domain size and scaling, results from our model can be correlated with cortical folding diseases such as lissencephaly and microcephaly.

Poster Session - Board: 702 / 36

The response of net primary production to future climate change and CO₂ under RCP4.5 in China

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In this study, the maximal extent of future NPP uncertainties are explored by employing the conditional nonlinear optimal perturbation related to parameters (CNOP-P) approach and the Lund-Potsdam-Jena (LPJ) model based on future climate change assessments, which are provided by 10 general circulation models (GCMs) of the Coupled Model Intercomparison Project 5 (CMIP5) under the Representative Concentration Pathway (RCP) 4.5 scenario at the North-South Transect of Eastern China (NSTEC). We find that the future NPP will increase due to climate change and CO₂; however, there is a difference in the extent of the variation resulting from the 10 GCMs and the CNOP-P approach. Future NPPs are estimated from 3.89 Gt C (MRI-CGCM3 model) to 4.51 Gt C (bcc-csm1-1 model) using the LPJ model driven by the outputs of 10 GCMs. The estimates of NPP with two types of CNOP-P-type climate change scenarios are 4.74 Gt C and 5.31 Gt C and are larger than other estimates of NPP. The above results imply that the terrestrial ecosystem supplies possible conditions for future carbon sinks for all climate change scenarios, especially for the CNOP-P-type climate change scenarios, although the estimates remain uncertain. Stimulative photosynthesis due to high precipitation and restrained autotrophic respiration due to low temperatures may play important roles in the carbon sink due to the CNOP-P-type climate change and CO₂ in all climate change scenarios. In addition, it is found that the combination of climate change and CO₂ is also a key factor in the increase of NPP.

Poster Session - Board: 510 / 463

Mass depending maze exploration strategy for true slime mold

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True slime mold *Physarum polycephalum* is a large uni-cellular amoeba-like organism and it can sense environmental information and change its behaviours. Large true slime mold extends its frontal parts for foraging. To study its exploration strategy, we observed how *physarum* spreads in a *binary-tree-shaped* maze. We found that slime mold changes its searching strategies when its total mass changes. To explain this result, we made a new mathematical model which consists of cylinders filled with liquid, periodic contracting active springs, tubes connecting between cylinders and the elastic sheet. In our model, the pressure has an important role to transmit information among frontal parts. Our model reproduces fundamental characteristics of the front expanding and the searching behaviours of slime mold.

Poster Session - Board: 809 / 496

Reconstruction of the complex trajectories of cell developments based on single-cell RNAseq data

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The unprecedented accumulation of high-throughput single-cell RNAseq data provides an essential opportunity for researchers to study the dynamics of biological systems. At the same time, it raises new questions and grand challenges in view of the key characteristics of these data that include high-dimensionality and heterogeneity. In response, we develop a data-driven computational framework to map and reconstruct of dynamical trajectories of cell based on the high-dimensional molecular profiles from snapshot single-cell data. By integrating tools from topological data analysis (level-set method) and the nonparametric statistics, we first perform nonlinear dimension reduction on the data to construct the cell developmental landscape, and then reconstruct the complex trajectories by finding the cell state transition path on the landscape. We apply this method in the analysis of cell developmental processes and provide novel insights into the field of mathematical and computational biology.

Poster Session - Board: 508 / 321

A common theory for proportion regulation in animals

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One of the fundamental problems in biology would be the method by which organisms can regulate a distribution in response to global information. For example, a cluster of organisms can regulate the proportion of individuals that perform various roles or modes as if each individual is aware of the overall situation without a leader. Slow or rapid self-organized pattern formations with time evolution on animal skins might also be one of the processes of ratio regulation of pigment cells. Thus, in various species, a specific ratio exists at multiple levels, from the process of cell differentiation in multicellular organisms to the situation of social dilemma in a group of human beings. In this study, we consider individual that means a particle who has a certain size and internal mode, then propose a common basis for regulating collective behaviour that is realized by a series of local contacts between individuals. The most essential behaviour of individuals is to change their internal mode by sharing information when in contact with others. Our numerical simulations and analysis for regulating the proportion in two kinds of modes show that asymmetric properties in local contacts are essential for adaptive regulation in response to global information. In this poster, some actual examples of proportion regulation are described and applicability of our theory would be verified. We will discuss that this simple mechanism of this theory could indicate that well-organized groups in nature can be regulated through local contacts only.

M. Iwamoto & D. Ueyama, "Basis of self-organized proportion regulation resulting from local contacts", *Journal of Theoretical Biology*, 440 (2018) 112–120.

Poster Session - Board: 251 / 147

Stability analysis of a mathematical model with distributed delay

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Gene expression and genetic regulatory networks (GRNs) have become important areas of study because they play an important role in solving issues related to human health such as cancer diseases. Cancers can be hard to recognise and the best way to improve their defected is to understand the underlying mechanisms of genetic regulatory dynamics. This means introducing and improving mathematical models of GRNs to reflect oscillatory phenomena. In this work, we propose a lac operon model with time delay and nonlinear degradation rate for mRNA and investigate the nonlinear dynamical behaviour arising from the model, such as stability and Hopf bifurcation of the equilibrium, by taking the average delay as the bifurcation parameter. From the dynamical behaviour of this system: the equilibrium is stable in the absence of delay or when the delay is small; as time delay increases gradually then the stability changes and Hopf bifurcation happens. Then reverse a Hopf bifurcation to translate the equilibrium of the system from unstable to stable steady state.

Poster Session - Board: 511 / 535

Quantifying convergence of the Kingman coalescent via the ancestral process per generation

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Error threshold being the forefront of the issue for computationally-intensive methodologies and statistical models based on Kingman's coalescent, six main points arise: (i) discrepancy between the exact and linearized non-coalescence probability; (ii) validity of the linearized coalescence probability; (iii) conditional probabilities of single-pair and multi-coalescences given at least one coalescence; (iv) parity of reduced ancestral processes that suppress multi-coalescences, when compared to the exact ancestral process; (v) genealogical topology; and (vi) subsequent inter-arrival times. Regions of adherence and detraction from the Wright-Fisher ancestral process were identified, in terms of transition probabilities and expected inter-arrival times, due to the linearization of Kingman's coalescent that neglects multi-coalescence events. Empirically, expected genealogical parity of the single-pair restricted Wright-Fisher haploid model exceeds 99% where $n \leq \frac{1}{2} \sqrt[3]{N}$; similarly, per expected interval where $n \leq \frac{1}{2} \sqrt{\frac{N}{6}}$. Quantitative parametric analysis on the varieties of multi-coalescence events in restricted Wright-Fisher models, rather than stochastic realization, avoids elaboration of the genealogical sample space under multi-coalescence. Mutational activity, such as site frequency spectra, will not be accurately measured with the Kingman coalescent when sample sizes exceed these criteria.

Poster Session - Board: 118 / 464

The analysis of the effect of cell dynamics on Delta-Notch interaction during retina vasculature development

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Pattern formation by Delta-Notch interaction has been well studied experimentally and theoretically. The Delta-Notch system is observed in various pattern formation process such as somitogenesis, neuroendocrine cell differentiation in lung, T cell differentiation and blood vessel development. Recent studies have shown endothelial cell proliferation and movement happen during this process. However, to our knowledge, there is little theoretical research about the effect of cell dynamics on Delta-Notch interaction.

In the present study, we examined the effect of cell dynamics on Delta-Notch pattern formation during retina vasculature development. We incorporated cell movement and proliferation to the model for Delta-Notch interaction. Using the model, we analytically derived the instability condition and numerically generated the patterns which have the similarity with the three patterns observed in vivo. It is difficult to capture the dynamics of cell movement and proliferation with standard linear stability analysis of fastest growing wavenumber component. Therefore, to consider all wavenumber components, we introduced the instability index, $\Psi(t)$, as the mean of square of Delta expression values. Based on Parseval's theorem regarding discrete Fourier analysis, we can derive that $\Psi(t)$ is equivalent to the average of power spectrum. Therefore, by considering the values of power spectra, we can evaluate the instability of the system.

$$D_x = \sum_{m=0}^{n-1} \delta_k e^{\lambda_k t + i k x}$$

$$\Psi(t) := \frac{1}{n} \sum_{x=1}^n D_x^2 = \frac{1}{n} \sum_{m=0}^{n-1} |\delta_{\frac{2\pi m}{n}}|^2$$

D_x is the expression values of Delta, δ_k is the discrete Fourier transform of D_x , n is the number of the cells, $k = \frac{2\pi m}{n}$.

These analyses and numerical calculations suggest that the vasculature which express homogeneous pattern shows high motility and proliferation rate of their endothelial cells. Based on these theoretical results, we experimentally observed cell dynamics during retina vasculature development by organ culture and immunohistochemistry. The results showed random endothelial cell movements and proliferations happened more frequently in vein than in artery, which are consistent with analytical and numerical results. These results suggest that cell dynamics affect artery-vein differentiation via Delta-Notch interaction.

Poster Session - Board: 512 / 537

Analyzing sleep patterns of shift workers via Phillips-Chen-Robinson model (PCR-model)

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Increments in around-the-clock service in modern society yield increments in shift work. As a result, nowadays more than 20% of population in the world work in shifts. As shift work schedules inevitably have increased, the risks of shift work are also presenting including the increment of risk for disease, such as cardiovascular-disease and cancer. There have been several approaches to analyze effect of shift work through mathematical modeling, however few studies have applied mathematical modelling to actual data. Here, we applied the Phillips-Chen-Robinson model (PCR model),

one of the human sleep process models, to analyze actual data of nurses who work in Samsung-hospital. We modify the PCR model with light actigraphy of nurses who work shifts to fit irregular and personal sleep/wake timing. As a result we find a critical factor which has strong correlation with sleep quality. By using this factor we find a new sleep model which provides best sleep time to achieve the best sleep quality.

Poster Session - Board: 504 / 109

Mathematical modelling of tissue growth in a spatially-varying permeability tissue engineering scaffold

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Tissue engineering is a rapidly growing field, attracting a huge concentration of research effort. An important subfield of tissue engineering focuses on the use of bioreactors, devices that attempt to simulate a physiological environment in order to promote the growth of functional cell or tissue *in vivo*. In this talk we present a mathematical model to simulate both nutrient transport and cell proliferation within a spatially-varying permeability scaffold inside a perfusion bioreactor, and compare results from this model with experimental results from the literature.

Poster Session - Board: 211 / 316

Uncertainty quantification of HIV dynamics using hierarchical models

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It is an interesting topic to predict how dynamics change in disease progression. Our goal is to predict dynamics of the vital cells in the human immune system using the hierarchical HIV models. We assumed that the parameters are random variables with intra-level noise and inter-level noise. Individual-level parameters of HIV model are estimated by generalized least squares method based on the field data. At the population-level, it is not desirable to estimate joint distribution of all the parameters because of computational cost and overfitting. Thus, we build a model by estimating the distribution of only a few selected by the parameter reduction using the sensitivity matrices. Then, we estimate the joint probability distribution of remaining parameters employing algorithms for population parameter estimation. Finally, we solve ordinary differential equations with random coefficients to predict the dynamics of target cells.

Poster Session - Board: 711 / 526

Use of data assimilation to infer the effects of sink strength on plant carbon balance processes

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Predicting the carbon balance of terrestrial plants, and its vulnerability to environmental change, is a fundamental problem common to agriculture, ecology and ecosystem science. Plant productivity is fuelled by the carbon taken up during photosynthesis, but other limitations to growth may restrict the ability of plants to utilise this carbon in production, a phenomenon known as sink limitation. Understanding how sink limitation affects the carbon balance of plants is one of the key challenges to developing better predictions of productivity. Here, we applied data assimilation (DA) to an experiment in which sink limitation was induced by restriction of the rooting volume of *Eucalyptus tereticornis* seedlings, in order to infer how carbon balance processes were affected. The ultimate goal of our study was to examine how carbon balance models should be modified to represent sink limitation of growth, whilst maintaining mass balance.

Our results demonstrate that several process representations need to be modified, including a clear need to incorporate a temporary storage pool of carbon as non-structural carbohydrate (NSC), with a dynamic utilization rate for growth. We were able to infer that, in addition to a reduction in photosynthetic rates, sink limitation reduced the NSC utilization rate, increased growth respiration, modified the carbon allocation pattern and accelerated senescence. The attribution analysis indicated that all of these process responses contributed significantly to the overall reduction in biomass observed under low rooting volume. Our DA-model analysis of this root volume restriction experiment provided significant new insights in the response of key carbon balance processes to sink limitation. Applying this approach more broadly would potentially allow us to identify general patterns in these responses that could then be formulated for inclusion into models. Overall, this approach provides important insights into the relationship between carbon uptake and plant growth, and could significantly advance our models of vegetation responses to global change.

Poster Session - Board: 210 / 294

Feedback control of epidemic models using Hamilton-Jacobi-Bellman equation

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In this research, we study feedback control problem in the context of deterministic epidemic models. Feedback control is obtained by solving Hamilton-Jacobi-Bellman(HJB) equation, which is employed to overcome limitations of previous work. There are three key factors in the implementation of this methodology, decoupling value function and control variables, truncation of unbounded domain, and numerical solver for 1st order hyperbolic PDE. While this approach seems complicated, it has an obvious advantage in generalization to stochastic optimal control problem. With proper treatments for technical challenges, we provide a tool that can be widely applied.

Poster Session - Board: 109 / 255

Beyond the knock-out: float through the cytosol, sting like p53

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p53, a cellular damage response regulator, is mutated in 50% of all cancers. We have constructed a mathematical model showing how different p53 dynamics after UV radiation and γ -irradiation exposure allows cells to respond properly to both slowly and quickly detected damage. We extend this model with an apoptosis module accounting for the transcription-dependent and -independent activities of p53, which is then used to analyze and classify contrasting apoptosis evasion strategies in commonly used tumour cell lines. In particular, we predict that lower levels of basal p53 contribute to the radiosensitivity observed in many cancers, and that self-overregulation of p53 is only one of many ways in which gain-of-function p53 mutations can be advantageous to tumour cell survival. Moreover, the downregulation of p53 by its canonical antagonist, Mdm2, has been well-studied in the nucleus, but this same interaction in the cytosol may be responsible for weakening the transcription-independent p53 pathway in humans. These models provide a unified framework for studying the broad and surprising array of effects of p53, far beyond the loss-of-function mutations well-known across cancers.

Poster Session - Board: 401 / 208

Male mating strategies and primate monogamy

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Primates exhibit an array of mating behaviours and arrangements, from monogamy to promiscuity, or mate-guarding to multiple-mating. We have previously explored the role of adult sex ratio in determining the likelihood of males choosing either promiscuity or monogamy, but many questions remain open. In particular, do (and, if so, *how* do) longevity and life history contribute to the choice of male strategy? And how can we characterise the effectiveness of guarding for those males who employ that strategy? We examine some of the trade offs that arise, and how they can influence the choice of male strategy.

Poster Session - Board: 104 / 33

Stochastic models of cell invasion with fluorescent cell cycle indicators

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Fluorescent cell cycle labelling in cell biology experiments provides real time information about the location of individual cells, as well as the phase of the cell cycle of individual cells. We develop

a stochastic, lattice-based random walk model of a two-dimensional scratch assay where the total population is composed of three distinct subpopulations which we visualise as red, yellow and green subpopulations. Our model mimics FUCCI technology in which cells in the G1 phase of the cell cycle fluoresce red, cells in the early S phase fluoresce yellow, and cells in the S/G2/M phase fluoresce green. The model is an exclusion process so that any potential motility or proliferation event that would place an agent on an occupied site is aborted. Using experimental images and measurements we explain how to parameterise the stochastic model, and we apply the stochastic model to simulate a scratch assay performed with a human melanoma cell line. We obtain additional mathematical insight by deriving an approximate partial differential equation (PDE) description of the stochastic model, which leads to a novel system of three coupled nonlinear reaction diffusion equations. Comparing averaged simulation data with the solution of the continuum limit description shows that the PDE description is accurate for biologically-relevant parameter combinations.

Poster Session - Board: 309 / 425

Influencers in ant colonies revealed by temporal network analysis

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Information transfer is thought to play a key role in adaptive complex systems such as social insects, brain and human society, while epidemic spreading through interactions can impact on survival in the individuals and society. Social insects such as ants and bees are one of the most sophisticated complex systems exhibiting collective decision making, providing us the opportunity of studying how the information transfer and disease spreading occur through the interactions. Recent advances in tracking systems enable us to collect quantitative and massive data of each individual and interactions in a colony. A recent empirical study [1] used an automatic tracking method based on image analysis, and revealed rapid spreading dynamics in honey bee colonies. However, the attributes of each individual including age, caste, and activity were not considered, although such heterogeneity of individuals may be crucial for the adaptability of the colony. Thus, the relationship between the heterogeneity in the colony and the spreading dynamics is less understood. In the present study, we used an image-based tracking system (Bugtag; Robiotech Inc.) to detect the movements and interactions of ants (*Diacamma sp.*). To reveal the relationship between the spreading dynamics and the heterogeneity in individual attributes, we investigated how interactions spread the information or diseases by using temporal networks which are promising tools for understanding spread dynamics, and then quantified heterogeneity in individual attributes such as age. The results show that the spreading was more rapid than randomized data conserving degree sequence, and younger individuals tended to be influencers which promoted the rapid spreading. We will discuss the adaptive significance of the relationship between rapid spreading dynamics and differences in individual attributes.

[1] Gernat, Tim, *et al.* "Automated monitoring of behavior reveals bursty interaction patterns and rapid spreading dynamics in honeybee social networks." *Proceedings of the National Academy of Sciences* 115.7 (2018): 1433-1438.

Poster Session - Board: 102 / 24

The role of cytoplasmic proteins on cell polarity formation of asymmetric cell division

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Asymmetric cell division is one of the widespread mechanisms for generating cell diversity, for which a mother cell creates a polarity in both membrane and cytosol. In both experiment and theoretical approaches, PAR polarity of *C. elegans* embryo has been extensively well-studied and it was found that Anterior-Posterior (AP) polarity of cell membrane proteins plays a crucial role in determining cell asymmetry. However, most of previous studies have not considered the role of cytoplasmic proteins on AP polarity formation, although AP polarity is occurred with a tight regulation of both membrane and cytoplasmic proteins such as MEX-5/6 and PAR-5. Here, we develop a multi-dimensional polarity model including cell's geometrical property and show how the cytoplasmic protein plays an important role in creating a robust AP polarity. We also show that the cell geometry can give a critical effect on AP polarity, and the temporal and spatial regulation for the robust AP polarity is based on the harmony of biochemical, mechanical, and cell geometric properties.

Poster Session - Board: 208 / 282

Bifurcation analysis of an epizootiological model of avian malaria

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Avian malaria is a mosquito-borne parasitic disease of birds caused by protists of the genera *Plasmodium*, most notably *Plasmodium relictum*. This disease has been identified as a primary cause of the drastic decline and extinctions of endemic birds on Pacific Islands. In this work, we formulate an epizootiological model of the transmission dynamics of avian malaria between a generic bird species and mosquito using a system of ODEs. We derive the basic reproduction number as well as criteria for the existence and stability of disease-free and enzootic equilibria. We discuss strategies for minimizing the impact of avian malaria in two scenarios: disease-free populations which may be invaded by avian malaria and populations where this disease is enzootic but where bird species have not developed resistance.

Poster Session - Board: 311 / 504

Stochastic-Spatio-temporal lattice (SSTL) Models of tree infestation

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Using a simple lattice model describing infectious tree disease dynamics on a homogeneous landscape we can observe an Epiphytotic phase transition from local confinement of the pathogen to a global epidemic through the forest. The phase transition can be understood in terms of the forest tree density and the pathogen virulence. One interesting application of the model involves capturing the pathogen spread-velocity and applying simple statics to pre-empt the phase transition into the Epiphytotic regime. Theoretically this yields an early warning system. The early warning phase transition could potentially be utilised to inform control strategies and negate system wide devastation of plant species.

Poster Session - Board: 119 / 511

Transport of intermediate filaments in cells

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Recently, it has been shown that intracellular transport of assembled intermediate filament proteins is one major determinant of their organization in cells. Based on experimental data, mathematical models of the spatio-temporal distribution of intermediate filaments in cells are developed to investigate the contributions of different types of transport such as retrograde flow of actin and motor proteins. Furthermore, models for the motion of single filaments driven by motor proteins are also proposed.

Poster Session - Board: 402 / 324

On mathematical standard structure of a binary digit of memory in a cell and its application to biological or life science phenomena

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A mathematical standard structure of a binary digit of memory in a cell is presented. This is based on a kind of frequency model with scale effect. This model has ability of “on-off” switching property, and moreover, this is affected by scale effect to make the memorable ability be reinforced. This property is derived from multiple covalent modification cites inducing important enzyme reaction, which is represented by the Michaelis-Menten type nonlinearity.

Some examples of application is also presented. One example is Cyanobacterial allosteric circadian rhythm of *Synechococcus*. Another is about Biological Nitrogen Fixation ability of *Nostochineae* cyanobacteria. I will explain briefly that scale effect affects the phenomena effectively to make the system be robust.

Poster Session - Board: 207 / 279

The effect of environmental variability and periodic fluctuations on disease outbreaks in stochastic epidemic models

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Seasonality and contact patterns due to environmental fluctuations and social behaviour affect the dynamics of disease outbreaks. Recent studies applied to deterministic epidemic models with periodic environments have shown that the average basic reproduction number is not sufficient to predict an outbreak. We extend these studies to stochastic epidemic models with periodic environments to investigate the combined effect of periodicity and variability on disease outbreaks. The deterministic models are extended to continuous-time Markov chain and stochastic differential equations. A numerical study of the dynamics of several stochastic SIR and vector-host models with environmental variability and periodicity are investigated in terms of probability of an outbreak.

Poster Session - Board: 108 / 99

The influence of molecular reach and diffusivity on the effectiveness of membrane-confined reactions

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Tethered enzymatic reactions are a key component in signalling transduction pathways. It is found that many surface receptors rely on the tethering of cytoplasmic kinase to initiate and integrate signalling. A key factor to such reaction is the molecular reach; however, the role of it is incompletely understood. To date, a large number of compartment-based ODE and stochastic models have been developed to study this problem. In recent years, spatial-stochastic models have emerged as a more realistic representation for such processes, among which lattice-based stochastic reaction-diffusion models are a popular approach for studying complex spatio-temporal processes inside cells. To understand the role of molecular reach in tethered signalling, we employed an accurate and convergent lattice-based stochastic reaction-diffusion model (CRDME). We find that the molecular reach can increase or decrease biochemical reactions depending on the diffusion coefficient in 2D membrane but not in 3D cytosol.

Poster Session - Board: 703 / 122

How do the dynamics of carbon and nitrogen allocation impact plant growth?

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Improving crop yield is essential to meet increasing global food demands. Crop yields depend on the coordinated acquisition of carbon and nitrogen by the leaves and roots respectively and the use

of these nutrients within each part of the plant. Changes in environmental conditions cause fluctuations in carbon and nitrogen availability. This leads to crosstalk between the signalling pathways for carbon and nitrogen. Carbon- and nitrogen-derived signals have been observed in plant growth, but how these signals cooperate together with changes in nutrient availability is still unknown. Here, we discuss the implementation of such feedback mechanisms using a carbon and nitrogen transport model for plant growth.

Poster Session - Board: 103 / 25

Mathematical modelling of cytosolic liquid-liquid phase separation

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Intracellular phase transitions are an emerging mechanism for cell organization. These membraneless compartments are formed via liquid-liquid demixing and subsequent concentration of cellular components in a specific region. By undergoing these localized phase separations, cells are able to create dynamic compartments that help maintain the regulation of biomolecular interactions and localize factors such as RNAs and proteins. The utility of liquid-liquid phase transitions and the assembly of cytosolic compartments is especially critical in large, multinucleate cells. These types of cells are common in the biosphere and include skeletal muscle tissue, the placenta, many filamentous fungi, and certain types of cancer. A powerful model organism for studying liquid-liquid phase separations (LLPS) is the branching, multinucleate fungus *Ashbya gossypii*. In *Ashbya*, Whi3, a polyQ tract-containing RNA binding protein, binds to and localizes multiple different mRNAs by forming liquid-like droplets in the cell. Under normal physiological conditions, Whi3 alone cannot form liquid droplets, *in vitro*, as this is a phenomenon that only occurs once it is able to bind with RNA. However, how Whi3 and RNA combine to form complexes and how these complexes influence droplet properties remains elusive. This issue is further complicated due to the many possible subcomplexes of RNA and protein that can exist. Specifically, the target RNAs have multiple binding sites for the Whi3 protein and the Whi3 protein has two possible RNA binding sites and likely interacts with itself using the polyQ tract. This means that there are many possible types of interactions between components. Additionally, while preliminary work within the Gladfelter Lab has shown that there is a fairly consistent average ratio of Whi3 to RNA in each droplet of a population, it is unclear what distribution of the different protein-RNA combinations gives rise to this average ratio. To understand the role that the different combinations of Whi3 and RNA play in the initial phase separation and the properties of the droplet population, such as size, shape and spatial distribution of droplets, we have created a mathematical model that employs the use of the phase field method. With phase variables to represent the volume fractions of Whi3, RNA, and the complexes they form, we propose a model that employs the use of mass action kinetics and a modified double-well free energy to represent the complex dynamics present in the cytosol. We report modelling and experimental progress on these cytosolic liquid-liquid phase separations in *Ashbya* as they help guide our understanding of the mechanisms behind droplet formation in the cytosol, as well as how these droplets function in cellular regulation.

Poster Session - Board: 116 / 404

Modelling of intracellular calcium responses in the presence of dynamic stimuli

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Calcium is a universal messenger that participates in a great variety of physiological functions including muscle contraction, neuronal plasticity and immune responses. There is now compelling evidence that transient changes in the intracellular calcium concentration are key for achieving such versatility.

To date, most of these findings have been obtained from constant stimulation or step change protocols. However, under physiological conditions, cells often experience time dependent stimuli such as transient changes in neurotransmitter or oscillations in hormone concentrations. How cells transduce such dynamic stimuli into an appropriate response is an open question. We exposed HEK293 cells and astrocytes to dynamically varying time courses of carbachol and ATP, respectively, and investigated the corresponding cellular calcium activity. While single cells generally fail to follow the applied stimulation due to their intrinsic stochasticity and heterogeneity, faithful signal reconstruction is observed at the population level. We provide a number of transfer functions that translate the extracellular stimuli into the ensemble calcium spike rates. By computing the mean root square error between the predicted responses (based on the transfer functions) and the actual responses, we identify a simple leaky integrator model as a powerful approach. For this, we show how to invert the transfer function to estimate the stimulus that should be applied in order to achieve a specific response. Throughout the analysis we pay particular attention to the non-stationarity of both the applied stimuli and the calcium responses.

Poster Session - Board: 202 / 40

Analysis and simulation of a mathematical model for rabies transmission in the Philippines

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Rabies is a fatal zoonotic disease and remains to be a priority health concern in the Philippines. Dogs remain to be the principal carrier of rabies and despite the fatality of rabies, it is a vaccine-preventable disease. Currently, the Philippine health officials have been conducting mass dog vaccination campaigns with the goal of having a rabies-free Philippines by the year 2020. However, statistical information about the disease poses a challenge and gives rise to doubts on whether the goal is achievable. In line with this goal, our aim for this study was to see whether eliminating dog rabies in the country is possible. Here, we developed a simple mathematical model, following the SEIR framework, that describes the dynamics of rabies infection among dogs in the presence of mass vaccination wherein some model parameters were calibrated from actual data sets. We used the model to predict the long-term rabies incidence and to analytically find an expression for the basic reproduction number in terms of vaccination rate, dog reproduction rate, transmission rate, and rate of vaccination immunity loss. By numerical simulations, we were able to determine the parameter combinations or scenarios for zero rabies infection. We assessed the validity and feasibility of these scenarios via data analysis. Our preliminary findings pointed to mathematical modelling as an important tool to make realistic projections about the rabies disease.

Poster Session - Board: 257 / 441

Bifurcation analysis of cervical cancer mathematical modelling

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In Noor Asih *et al.* (2016) already given mathematical modelling as the dynamic of HPV infection on cervical cancer. Also given five scenarios for the existence of equilibrium points and their local stability. From the analysis of the system it is found the basic reproduction number is depends on the infection rate, the number of new virion that produce by infected cells, the death rate of virus, the growth rate of infected cells and progression rate. The existence and the local stability of equilibrium points are depend on basic reproduction number, the growth rate of pre-cancer cells and invasion rate. So we predict that there are some bifurcation parameters on that model. While we do some simulation by continuing those parameters we found some bifurcation such as fold bifurcation, cusp bifurcation and zero Hopf bifurcation. Further we analyze domain of each bifurcation parameter.

Poster Session - Board: 203 / 131

Ranking dose-normalized antiviral effect of drug combination treatments against hepatitis C virus

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Since many kinds of Direct Acting Antivirals (DAA) have become the main treatment instead of interferon- α (IFN- α) against hepatitis C virus (HCV), combinations of these DAA are now standard treatment strategies. These treatments are very effective, however, at the same time, this provokes the problems which drug combination is more or most effective for each patient. Therefore, we established a viral replicon system for HCV to quantify the efficacy of each drug or drug combination easily. In this study, we used 15 different kinds of DAA (telaprevir, danoprevir, asunaprevir, simeprevir, sofosbuvir, VX-222, dasabuvir, nesbuvir, tegobuvir, daclatasvir, ledipasvir, IFN- α , IFN- λ , cyclosporin A, and SCY-635) and quantified the efficacy of (single and) multiple drug combinations using the replicon system. Then, we calculated instantaneous inhibitory potential (IIP) which captures the effectiveness of each drug combination as a function of the drug concentration. Furthermore, we defined and calculated the critical concentration index (RCI) that achieves 95% reduction in HCV replication is shown for each drug combination. The RCI intrinsically varies among the drug combinations. As an example, we found SMV&IFN- α yielded the lowest RCI values among the tested double-combinations. We would like to further discuss how our framework could enable drug usage optimization by quantifying the antiviral activity in preclinical settings, and presenting basic evidences for cost-effective drug selection.

Poster Session - Board: 406 / 410

Identification of regulatory enhancer regions

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In genetics, enhancer regions are short non-coding strands of DNA belonging to a class of elements known as cis-regulatory. These regions, typically in intergenic regions, encompass binding sites for proteins (transcription factors) that regulate gene expression. Changes to the DNA sequence in these enhancer regions are thought to provide a mechanism to explain changes of gene expression even though the genes across species may display some sequence conservation.

The challenge in the identification of these enhancers is that, unlike protein-coding genes, they do not follow a clear genetic code. Sequence conservation across species is often used as a proxy to identify regulatory regions with the rationale that functional elements are under some evolutionary pressure to maintain biological function and, hence, less subject to mutations. However, there is emerging evidence that functional non-coding sequences that show conservation of biological function in the combination of transcription factor binding sites but show little to no conservation at a sequence level using traditional alignment tools. Hence, our ultimate goal is the identification of conserved non-coding sequences by alternative methods to “traditional” sequence alignments.

In this work, we obtain an alignment between the DNA assemblies of human (hg38) and mouse (mm9) around the gene *tbx5* and perform a cursory statistical analysis to identify and classify non-coding functional regions. The model is developed in a Bayesian framework and we obtain a segmentation using the segmentation classification algorithm, *changept*. The algorithm samples segmentations using a Markov chain Monte Carlo method that generalises the Gibbs sampler. We aim to incorporate a diverse set of data types into the model to increase accuracy and applicability.

Poster Session - Board: 507 / 315

Predator-prey interactions in wastewater treatment plants

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The activated sludge process (ASP) is the most widely used process for the biological treatment of both domestic and industrial wastewaters. Wastewater treatment plants (WWTPs) based on the ASP are in widespread use in both developed and developing countries.

The ASP uses microorganisms which grow by consuming organic pollutants that are present in the wastewater. This produces new organisms whilst simultaneously cleaning the wastewater. The microorganisms flocculate to form settleable solids, the ‘activated sludge’.

Central to the success of the ASP is the activated sludge. However, a significant drawback of the ASP is the production of excess ‘sludge’. The expense for treating this can account for 50–60% of the total operating costs in a WWTP. Traditional methods for disposing of excess sludge are becoming increasingly unattractive due to a combination of increasing land costs and environmental concerns about the presence of toxic elements. Thus there is a growing interest in methods that reduce the volume of excess sludge produced by the ASP.

A promising method to reduce sludge formation is to introduce a higher order organism, such as protozoa or metazoa, into the system which predate upon the microorganisms. This is potentially

very attractive, since once the predators have been released into the reactor there are no 'running' costs.

Why does predation reduce sludge? The ASP can be considered to be a food-chain, in which the biomass extracts mass and energy from the substrate. The introduction of a predator introduces a new layer into the food-chain: mass and energy are now transferred from the microorganisms to the predator. At each step in the food chain not all of the available energy and material are transferred to the next level: some energy, a significant proportion of the energy, is used for maintenance processes, respiration and reproduction. Thus predation on microorganisms may lead to a lower total biomass, i.e. sludge reduction.

Predation has been shown to be an effective technique in lab-scale experiments and pilot-scale systems. Although a variety of predators could be used, much attention has focused on the use of worms. Worm growth is clearly a prerequisite for sludge reduction through predation. Relatively little is known about the growth and development of worms during sludge predation. However, it has been shown that the wrong choice of aeration rate, temperature and predator (worm) density can adversely effect worm growth and consequently sludge reduction.

One of the main barriers to the adoption of predation as a cost-effective mechanism to reduce sludge formation is the phenomenon of uncontrollable growth of predators. Predator density in full scale plants can often reach very high densities. Associated with this is the well-known phenomenon of worm blooms, in which predator population densities display peaks followed by a sudden disappearance of the population. The development of methods to control worm proliferation is a challenging problem that needs to be overcome.

In this presentation a simplified model for a wastewater treatment plant is extended to include predators. Mechanisms which lead to the unsuccessful introduction of predators are identified.

Poster Session - Board: 110 / 263

Identifiability analysis in enzyme kinetics using profile likelihood

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The aim of this research was to explore the potential of profile likelihoods for identifiability analysis in the context of real enzyme kinetics data, collected ourselves.

Parameter identifiability concerns the question of whether the type of experimental data we have collected properly determines the parameters of our mathematical models. Identifiability issues arise because not all biological variables involved in the system can be measured, and even those that can be measured can be structurally decoupled from some of the parameters of interest. Although structural non-identifiability is in principle an all-or-nothing concept, in practice parameters may also be only weakly identified or may be practically non-identifiable given finite data. Profile likelihood has proven to be one of the few promising general methods of identifiability analysis that is applicable to multi-parameter, nonlinear problems, but it has not yet been widely adopted in the mathematical/computational biology community. Thus we sought to further explore its usefulness for typical models in this area, and using real experimental (as opposed to synthetic) data.

In this study, we collected data on the activity of the enzyme tissue plasminogen activator (tPA) under variety of scenarios, including different initial substrate and pH levels. We developed a series of simple reaction kinetics models, including both Michaelis-Menten velocity-concentration models and full time-dependent ODE models, and generated profile likelihoods under the various experimental conditions. For the simple Michaelis-Menten model we found that parameters were generally identifiable/weakly identifiable but tended to become less identifiable (approaching practical

non-identifiability) at lower pH levels. On the other hand, individual parameters of the full ODE model of enzyme kinetics showed full structural non-identifiability. This led us to consider the identifiability of targeted 'interest' parameters, motivated by the parameters in the simpler system. Using this approach we found that certain combinations of rate parameters, corresponding to those in the simpler Michaelis-Menten model, were better identified in the full model.

Overall we found profile likelihood to be a promising technique for identifiability analysis of enzyme kinetics models. For complex models, however, choosing targeted interest parameters appears to be essential to avoid structural non-identifiability. Further work is needed on systematically motivating these interest parameters based on, for example, simpler models and/or model reduction procedures. In the context of tPA kinetics, more complex reactions involving the inhibitor neuroserpin and interactions of H⁺ ions with the enzyme should be considered.

Poster Session - Board: 305 / 325

Dispersal heterogeneity and the spreading speeds of marine invasions.

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We propose a structured integro-difference equation model for an invasive marine species with a pelagic larval stage and examine the role of dispersal heterogeneity on the spreading speed. The spread of the green crab up the northwest coast of the Atlantic is used as a case study. We find that the relationship between spreading speed and demographic and dispersal parameters is similar to the relationship found in Fisher's equation. We also find that temporal variation in dispersal results in a faster spread rate than predicted by a time-averaged dispersal kernel. This is joint work with Lin Wang, Myriam Barbeau and Ali Gharouni.

Poster Session - Board: 117 / 436

Data analysis of single-HSC transplantation

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Hematopoietic system is maintained by hematopoietic stem cells (HSCs) with dual abilities of long-term self-renewal and differentiation to all types of blood cells. Recently, using a single-cell transplantation system and mice expressing a fluorescent protein, myeloid-restricted progenitors with long-term repopulating activity (MyRPs) were found. Moreover, by using paired daughter cell assay, MyRPs were directly differentiated from HSCs.

In this study, we investigated hematopoietic system incorporating the novel insight that there existed a cell type that exclusively differentiated to myeloid lineages. There were four types of populations in the model: (i) HSCs, (ii) MyRPs, (iii) progenitors, and (iv) differentiated cells. Differentiated cells includes B cell and T cell which are lymphoid cells and platelet, erythrocyte and neutrophil/monocyte as myeloid cells. Myeloid progenitors were produced via two ways, from HSCs directly and via MyRP

(myeloid bypass), after transplantation of a single HSC, while lymphoid progenitors were produced from only HSCs directly. This is the first study of investigating hematopoiesis with MyRPs.

We estimated some parameters which were growth rate, production rate and death rate using full data set of single-cell transplantation. From the result of data analysis, we will discuss the role of myeloid bypass after transplantation and the change of heterogeneity of HSC population with age.

Poster Session - Board: 209 / 288

The role of neutrophils in *Mycobacterium tuberculosis* infection

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Tuberculosis remains a widespread and deadly disease, infecting approximately two billion people worldwide. Gaining a better understanding of the immune response to *Mycobacterium tuberculosis* is crucial, and the increased prevalence of multi-drug resistant strains, the current complexity and length of treatment, and the inherent difficulties of experimental work each highlight the need for new approaches. Computational modelling of the complex immune response which results in the formation of lung granulomas can enable analysis of what is currently a relatively black box for scientists. In particular, the role of neutrophils in the granuloma response to *M. tuberculosis* infection remains largely unknown, as neutrophils are easily activated and short-lived, and thus pose unique experimental challenges to wet lab study. Through the incorporation of a neutrophil cell type into our existing hybrid agent-based computational model, we investigate the spatiotemporal dynamic formation of lung granulomas in response to *M. tuberculosis* infection. We are interested in determining how neutrophil presence induces both global and localized features of granulomas, the dynamics of neutrophil interactions with other cells and *M. tuberculosis*, whether the neutrophil response to *M. tuberculosis* is beneficial or detrimental to the host, and how that response can be harnessed to aid in therapies. Our goal is to not only identify the sufficient biological assumptions necessary to reproduce experimental datasets from our collaborators, but to shed insights on the mechanistic basis for neutrophil-directed immunopathogenesis in *M. tuberculosis* that are beyond current experimental capabilities.

Poster Session - Board: 214 / 433

Tracking the dynamics of multiple granulomas during infection with *Mycobacterium Tuberculosis*

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Infection with the bacteria *Mycobacterium tuberculosis* (Mtb) causes a dynamic immune response that spans multiple organs across multiple time scales. The infection may start with just a few Mtb infecting a few macrophages within the lungs, but sites of infection quickly experience local immune responses, and soon after draining lymph nodes become involved to mount an even greater defense. Different mathematical tools are required to simulate this complicated immune response, from the recruitment of the cells from the lymph nodes and their transport through the blood to the sites of infection, to the formation of granulomas, which are the hallmark of Mtb infection and are comprised of immune cells, bacteria, and other molecules. Agent-based modelling has been an effective multiscale approach to simulate the immune response during infection that forms a single granuloma. However, the computational cost of running these simulations begs for a quicker, coarser approach in order to study an infection across multiple granulomas within a single host lung. We propose a novel hybrid agent-based model that uses ordinary differential equations to evolve populations of cells, Mtb, and other molecules within each individual granuloma, that is then simulated as an agent within a whole-lung in silico infection model. The lung compartment can be connected to lymph nodes with granuloma agents spreading between compartments. This will allow for a higher-scale host response simulation to allow us to better address questions at the whole host scale and also be able to calibrate to datasets of whole human hosts.

Poster Session - Board: 215 / 452

Understanding the influence of tick co-aggregation on R_0 for tick-borne pathogens

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Tick-borne pathogens are transmitted when ticks take blood meals from vertebrate hosts. Ticks need to take blood meals to progress through immature life-stages and reach adulthood. For the most important zoonotic pathogens, including *Borrelia burgdorferi* (the causative agent of Lyme disease), two immature life-stages of the tick vector, termed larvae and nymphs, maintain the pathogens. Key features of tick feeding behaviour, and therefore of tick-host contact patterns, include the aggregation of ticks on hosts (whereby most ticks of a given life-stage feed on only a small minority of the hosts) and the co-aggregation of larval and nymphal ticks on the same minority of hosts.

A mechanistic network model is presented for tick-borne pathogen transmission that explicitly accounts for larval and nymphal tick co-aggregation and coincident coaggregation, also known as co-feeding. Co-feeding of nymphs and larvae allows transmission from an infected nymph to susceptible larvae feeding in close proximity and at the same time, but without the involvement of a systemic infection in the vertebrate host. By relating the next generation matrix epidemic threshold parameter R_0 to the in- and out-degrees of vertebrate host nodes in the mechanistic network model, a simple analytic expression for R_0 that accounts for the co-aggregation and coincident co-aggregation of ticks is derived. Simulations of Lyme disease transmission on finite realizations of tick-mouse contact networks are used to visualize the relationship between R_0 and the extent of tick co-aggregation.

The derived analytic equation explicitly describes the relationship between R_0 and the strength of dependence between counts of larvae and counts of nymphs on vertebrate hosts. Tick co-aggregation always leads to greater values for R_0 , whereas higher levels of tick aggregation only increases the value of R_0 when larvae and nymphs also co-aggregate. Aggregation and co-aggregation have a synergistic effect on R_0 such that their combined effect is greater than the sum of their individual effects. Co-aggregation has the greatest effect on R_0 when the mean larval burden of hosts is high

and also has a larger relative effect on the magnitude of R_0 for pathogens sustained by co-feeding transmission (e.g. TBE virus in Europe) compared with those predominantly spread by systemic infection of the vertebrate host (e.g. Lyme disease).

Co-aggregation increases R_0 , particularly in geographic regions and seasons where larval burden is high and for pathogens that are mainly transmitted during co-feeding. For all tick-borne pathogens though, the effect of co-aggregation can be to lift R_0 above the threshold value of 1 and so lead to persistence.

Poster Session - Board: 250 / 46

Genomic and immune features of anti-PD-1 response in diverse solid tumours

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Immunotherapy using checkpoint inhibitors has demonstrated clinical efficacy for cancers ranging from melanoma to non-small-cell lung cancer and other types. Despite some success, many patients do not respond to the therapy, and a subset of patients develops “hyper-progressive” disease. Biomarkers that predict response or toxicity to checkpoint inhibitors will help to select patients who are most likely to benefit from these novel immune agents. Clinical-grade next generation sequencing is becoming more prevalent, providing information about genomic alternations, which could serve as potential new biomarkers to immunotherapy agents.

In this retrospective study, we included 43 patients treated in a community cancer center who had diverse solid organ malignancies, completed sequencing of tumour DNA before the initiation of immunotherapy, and received at least one cycle of a PD-1 or PD-L1 inhibitor. Half of the patients had breast and gynecologic cancers, which have been less investigated for checkpoint blockade.

We found that response to checkpoint inhibitors was associated with i) fewer previous treatment lines, ii) longer duration of immunotherapy, iii) higher frequencies of peripheral blood monocytes and lymphocytes after treatment, and iv) higher tumour mutational burden (TMB). In addition, base substitutions and indels in PRKDC and LRP1B and amplification of BCL6 occurred more frequently in responders. PRKDC and LRP1B mutations showed significant association with higher levels of TMB, which was confirmed by large-scale cancer genomics data.

Results from this study may be used to inform patients who will have a better response to PD-1/PD-L1-based immunotherapy, possibly indicating a first-line therapy in their treatment.

Poster Session - Board: 252 / 205

Validating a mathematical model of brain tumour growth with the apparent diffusion coefficient

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The Proliferation-Invasion (PI) mathematical model of patient specific glioblastoma (GBM) growth utilizes T1 and T2-weighted/fluid attenuated inversion recovery (FLAIR) magnetic resonance (MR) images to estimate net proliferation (ρ) and net invasion (D) rates. We have previously developed methods to parametrize this model from these routine MRIs such that higher D/ ρ tumours are considered more invasive than lower D/ ρ tumours. More advanced MR imaging methods such as diffusion-weighted imaging (DWI) allow for the calculation of quantitative measurements. The apparent diffusion coefficient (ADC), which is calculated from DWI, is believed to be predictive of tumour cellularity and microstructure. Our objective is to validate that the PI model's measure of invasiveness D/ ρ derived from routine MRIs is consistent with quantitative MRI measurements. We hypothesize that D/ ρ will be correlated with the distributions of ADC values within the tumour. Further, we expect that the proportion of high ADC values (low cellularity) will predominate for low D/ ρ (highly invasive) tumours. T1Gd and FLAIR images were segmented and regions of interest (ROIs) created for patients with contrast-enhancing GBMs. A FLAIR penumbra ROI was created by excluding the T1Gd ROI from the corresponding FLAIR ROI. ROI's were then used to mask the co-registered ADC maps and the ADC values from within the ROI were plotted as a histogram. The ADC histogram from the FLAIR ROI was fit using a bimodal Gaussian model. ADC histogram peak boundaries were calculated as being \pm one averaged standard deviation from the averaged peak location (FLAIR ROI histograms). The averaged boundaries were then applied to each histogram. We calculated the percent of ADC voxels classified as being below each peak, within the lower or upper peak, within both peaks, or above the peaks. The percentage of voxels within each region were then plotted against D/ ρ . Understanding the relationship between D/ ρ and ADC allows us to connect observations on multiparametric imaging and elucidate the tumour biology. These results support the practical applicability of the PI mathematical model in quantifying patient-specific invasion characteristics by cross-correlating those findings with that seen on other imaging techniques and parameters, in this case ADC.

Poster Session - Board: 253 / 211

Regression of tumour cells in breast cancer administrating chemotherapy using MTD and metronomic techniques

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To gain deep insights into the interactions among major types of cells, such as healthy, tumour, and immune cells, in a tumour-bearing host, we propose a mathematical model consisting of four delay differential equations by considering the inherent delay in the tumour cells' life cycle. When choosing model parameters, sensitivity analysis justified previous assumptions had been considered.

Since the impact of immune system is decisive on the regression of tumour cells, stability analysis is performed for two different levels of immune system surveillance, that is, healthy and compromised tumour-bearing host.

Theoretically, it has been showed that in a healthy host the immune system is able to eradicate the tumour cells completely whereas in presence of weak immune system tumour cells have the opportunity to keep proliferating.

The latter case, necessitates an efficient treatment, and more precisely a combination of different treatments, for being able to fight and demise tumour cells.

Nowadays, Chemotherapy is the most common treatment which is administrated in various protocols. Among them, MTD (Maximum Tolerated Dosage) and Metronomic are of great significance in clinical observations. Our model suggests that Metronomic technique surpasses MTD after introducing this treatment. The last but not the least, since the results of mathematical experiments

illustrate the administrated Chemotherapy protocols are not able to eradicate the tumour cells, the proposed model unveils the demand for an adjunct treatment.

Poster Session - Board: 258 / 486

Mathematical models to predict clinically relevant events in cancer patients

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Cancer is one of the leading causes of morbidity and mortality worldwide. Many of the disease related events, such as metastatic progression, treatment resistance, and overall survival, generate much uncertainty and are oftentimes viewed as random. Applying current modelling techniques and methodologies to existing data can produce a forecasting framework that can be leveraged to predict these significant events that impact clinical decision making. We used a retrospective, longitudinal dataset of 3,505 patients with primary bladder cancer to build forecasting models that could be used prospectively in newly diagnosed patients. We built Markov models from individual patient progression pathways and used these models to simulate and predict future locations of metastatic spread. Additionally, we used machine learning techniques to temporally predict disease progression and overall survival. Analyzing the results of these models revealed that patterns of metastatic spread emerged in distinct subgroups of patients when stratified by gender and also by pathologic stage. Additionally, analysis of patient variables showed higher associations with both recurrence and survival for pathologic staging (post-operative) as compared to clinical staging (pre-operative). Incorporating additional longitudinal data such as treatment information and genomic data could lend to the predictions of therapy resistance and side effect development.

Poster Session - Board: 301 / 41

Stationary fronts in competition-diffusion models in randomly fluctuating environments

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The spatio-temporal intra- and interspecific competition of two diffusing similar populations is considered. The growth of both populations is either logistic or shows an Allee effect. Conditions of spatial segregation without mixing are investigated. Furthermore, the impact of density-dependent environmental noise on the occurring stationary fronts is studied. A special focus is set on the development of functions describing the density-dependent noise intensity. The obtained results are associated with a biological case study related to the competition of two invasive weeds.

Poster Session - Board: 303 / 185

Relating explicit spatial structure in population connectivity with biodiversity

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One of the challenging questions in Ecology is how spatial structure influences the formation of biodiversity patterns. Here, we explore networks that represent population connectivity including cases where dispersal is symmetric and asymmetric, looking for the relationship between population connectivity network structure and biodiversity patterns therein. In this metapopulation system, we simulate dispersal of individuals based on the probabilities given by a dispersal connectivity matrix, and measure resulting biodiversity.

Difficulties with this approach include the variety of possible network structures and the increasing complexity of networks as they become larger. To deal with this problem, we analyze and compare 1) theoretical networks of relatively small size, which vary in complexity, and 2) realistic large and complex networks that represents coral larval dispersal connectivities in a marine system. Through this approach, we will be better able to understand the possible contribution of geographical structure to biodiversity for metapopulations.

Poster Session - Board: 304 / 281

Elasticity analysis of random matrices in matrix population models

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Projection matrix models are known to provide us with a plenty of population statistics, such as population growth rate, steady size-class distribution, and sensitivity and elasticity for population growth rate. Hundreds of academic papers using the model have been published these last forty years and a database on many of their matrices is now available on the internet (COMPADRE and COMADRE), which contains the demographic data on more than a thousand species. Silvertown *et al.* (1996) published a famous paper, where they mapped elasticity vectors of survival, growth and fecundity for 84 plant species in a triangle simplex and found that they are located in a specific region. The same trend is found on the map for 1230 plant populations in the above plant database. To understand and clarify why they are located in a specific region, we constructed five types of random matrices. 4 by 4 random matrices were composed of two parts: fecundity and transition probabilities from a stage to another. The distribution of fecundities followed a Poisson distribution. The transition probabilities range from zero to one, whose row sums are less than 1. The elasticities for survival, growth and fecundity were calculated using 3000 random matrices and the elasticity vectors were plotted in the triangle map. The five types of matrices were as follows: (1) random matrices with no zero-element, (2) random matrices with no zero-element and the survival probabilities increase as individuals grow, (3) random matrices which have non-zero elements only on diagonal and sub-diagonal positions, (4) random matrices which have non-zero elements only on diagonal and sub-diagonal positions and the survival probabilities increase as individuals grow, (5) random matrices in semelparous species. The results are: (a) the distribution of the elasticity vectors moves to upper-left region of the triangle map as average of fecundity increases, (b) In the third and fourth types of random matrices, the distribution is located on a line whose slope is equal to 46 degrees. The slope can be described by a formula depending on the matrix dimension, n and ranges from 30 to 60 degrees with $n = 2$ to infinity. (c) In semelparous species, the distribution moves to the upper left along the 46-degree line. (d) There are no elasticity vectors in the bottom half of the triangle map.

Poster Session - Board: 307 / 366

What sort of interspecific interactions leads to deviation from a neutral community?

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The neutral theory in community ecology attempts to explain its species-abundance composition by the balance between local extinction of species due to demographic stochasticity and immigrational supply of new species from a meta-community. The original neutral theory is described by two parameters; the one (“theta”) that represents biodiversity in the meta-community, and the other (m) is the immigration rate. Quite surprisingly, such a two-parameter model often shows a good fit to real community data, leading to the impression that many real communities significantly look “neutral”. Inspired by the methodology in evolutionary game theory, here I try to reveal whether non-neutral communities with intra- and inter-specific interactions really look “neutral”, and if not, under what condition. My random community model explicitly incorporates those interactions and has new parameters that control the proportions of mutualistic (+/+), competitive (-/-), and exploitative (+/-) interactions in the community. Extensive computer simulations have revealed that communities that are rich with mutualistic interactions, or those with exploitative ones tend to look neutral although they are not, whereas those communities that have a mixture of competitive and exploitative interactions are often deemed non-neutral. Those results tell us limited statistical power in existing neutrality tests.

Poster Session - Board: 312 / 529

Comparing age- and stage-structured matrix models for declining species: case study with marine mammals

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IUCN criteria are the most authoritative and objective to assess the conservation status of animal species. Although IUCN criteria are purely descriptive in nature, they can be interpreted as e.g. the relative size of the annual population growth factor (λ , the dominant eigenvalue of a projection matrix). This enables quantitative assessment based on demographic data (survival and reproduction). However, such an assessment for many species is hampered since demographic data are often incomplete. To facilitate assessment when demographic data are incomplete we extended an existing framework (developed for species with a pre-adult stage of one year) to apply to species with pre-adult stages (=juvenile and sub-adult together) longer than one year. We develop both Leslie-matrices and stage-structured matrices and compare these with respect to eigenvalues, and both sensitivity and elasticity of underlying parameters. We illustrate our work with life history data and conservation status of a few marine mammal species.

Poster Session - Board: 302 / 156

A geometric model to explore multiple macroecological patterns across scales

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Macroecological patterns, such as the species area relationship (SAR), relative species abundance (RSA), and endemic area relationship (EAR) provide us useful information of ecosystem structures that can be applied to, for example, ecosystem conservations. To understand these patterns across spatial scales is one of the central challenges recent years. To tackle the challenge, we develop a spatially explicit geometric model where a set of species distribution ranges and individual distributions therein are described by spatial point processes. Essentially by calculating the number of individuals or distribution ranges given a sampling region, several well-known macroecological patterns are recovered including the tri-phasic SAR on a log-log plot with its asymptotic slope, and various RSAs such as Fisher's logseries and the lognormal distribution. In a simple manner, the EAR is also calculated in our framework. These multiple macroecological patterns can be derived with a single set of biological parameters, and therefore it may provide us a convenient way to discuss the multiple patterns in a consistent manner.

Poster Session - Board: 407 / 525

Menopause with a cause: The evolution of monogamy in response to female fertility loss

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The human species is unique in its tendency towards monogamy, a trait which can be traced back to hunter-gathering societies. Traditional explanations for this evolution have focused on the presence of paternal care and the needs of our offspring. However, recent research has challenged this claim, contending that the significant effects of mating competition on male choice result in evolutionary equilibria with little male care. This paper models the population dynamics of a rudimentary hunter-gathering society, and determines sufficient conditions for monogamy to supersede pure mating strategies as the optimal allocation of male reproductive effort. Utilising an approach based on the graphical analysis of systems of nonlinear ordinary differential equations, various situations were considered including the variation of reproduction rate, sex ratio and fertility loss. While our results concur with previous findings that male pair bonding triumphs in response to partner scarcity and male-biased populations, a dynamic expected gain model extended this reasoning to explicitly show that menopause and the age of menopause occurrence directly cause the evolutionary bias sufficient to cause a shift away from the multiple mating strategy.

Poster Session - Board: 403 / 328

Effects of population size and social connectedness on cumulative cultural evolution: A gene-culture coevolutionary model

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The demographic hypothesis of cumulative cultural evolution claims that population size has been a crucial determinant of the rate of cumulative cultural evolution in humans rather than other factors such as environmental risk. The original version of this hypothesis does not distinguish the role of population size from that of social connectedness, i.e. the degree to which individuals in a population

are socially connected with each other. Recently, one of our models showed that social connectedness may actually have a larger impact on the rate of cumulative cultural evolution than population size. However, these models all assume that the mode of learning which underlies cultural transmission is fixed and does not evolve, so that they cannot deal with the time scale of genetic evolution. In the present study, we extend previous models of cumulative cultural evolution by assuming that the allocations of the individual lifetime into two modes of learning, social and individual learning, co-evolve with the level of culture in the population. We derive the evolutionarily stable learning strategy, assuming that cultural evolution occurs on a faster time scale than genetic evolution. The results suggest that population size may have only a minor effect on the equilibrium level of culture realized by the evolutionarily stable learning strategy, while social connectedness may have a relatively large effect, conforming with the results of models without evolution of learning. These results indicate the importance of distinguishing different aspects of demography when modelling cumulative cultural evolution.

Poster Session - Board: 502 / 23

Modelling and optimal policy for decreasing Japanese empty homes, Akiya, due to an aging society

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Empty homes, called Akiya in Japanese, due to an aging population and declining birthrate is very serious problem in the aging society of modern Japan. The current proportion of empty home in Japan is 13.5%, but it is expected to be increased up to 30.2% nationwide in 2033, implying that Akiya will have a serious impact on the economy as well as the national finance. Indeed, Detroit city in USA was financially collapsed by 29.3% empty homes caused by the decline of the automobile industry. Currently, the Japanese government has started a countermeasure for decreasing the empty homes, but the effect is completely uncertain. Therefore, we here develop a mathematical model including an effective utilization of empty homes and consider the future transition of empty homes. Using the model, we suggest optimal policies by which we can reduce empty homes most effectively, with regard to government tax system and subsidy for the effective utilization of empty homes. This study shows a new framework of mathematical model to be applied for solving a social and economic problem in real world.

Poster Session - Board: 505 / 175

Marriage decision-making models based on male's willingness to cooperate on housework and childcare

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The unmarried rate of Japanese people is rising year by year, and countermeasures are required. We modelled male and female marriage decision-making models based on male's willingness to cooperate on housework and childcare. We assume that male marriage utility function decreases as male's willingness to cooperate on housework and childcare increases, while female marriage utility function increases. We also assume that a male decides to marry a female when his marriage

utility function is nonnegative, while a female does so when her partner's willingness to cooperate is at least the value that she demands. When both male's and female's conditions are satisfied, they get married. If they don't get married, the utility function is 0 for both males and females. Male's strategy is the value of his willingness to cooperate, and female's strategy is the value that she demands. There are Nash equilibria with marriage and without marriage. At Nash equilibria with marriage, both male and female marriage utility functions are positive and male's strategy is equal to female's. When the utility function changes by individuals, increase of marriage utility raises male's marriage fraction slowly in the all range and female's sharply in the range of large female marriage utility. We conclude that we should take countermeasures to all males and females with greater marriage utility to increase the rate of marriage.

Poster Session - Board: 509 / 456

Estimation of model parameters used to predict treatment response in breast cancer from dynamic contrast-enhanced MRI data using novel mathematical software

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Specific biomarkers can be identified in dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) breast scans and quantified using pharmacokinetic models that return estimates of parameters related to tissue physiology including vessel perfusion and permeability (K^{trans}), the extravascular-extracellular volume fraction (v_e), the plasma volume fraction (v_p), and the efflux constant (k_{ep}). In particular, K^{trans} and k_{ep} have been shown to be effective at predicting the response of cancer patients to treatment. Two fundamental issues in the field of DCE-MRI is the lack of standardization of the analysis and characterizing the time rate of change of the concentration of contrast agent in the vascular (the so-called "arterial input function" or AIF). We have recently developed a method for estimating accurate AIFs for the individual patients and associated software to automate the estimation of model parameters from DCE-MRI data taken from breast cancer patients using data that can be acquired routinely in community-based imaging centres.

Poster Session - Board: 105 / 66

Effects of different discretisations of the Laplacian in stochastic simulations

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A deterministic model of biochemical reaction networks is not always appropriate. Gene expression, for example, often involves a small number of molecules which means that noise can significantly influence the dynamics. By discretising space into voxels and letting the molecule dynamics be governed by the reaction-diffusion master equation, it is possible to model the reaction and diffusion of individual molecules on an arbitrary domain. Following on from the work of Meinecke and Lötstedt we apply a variety of numerical methods to the Laplacian operator in order to derive the jump rates that simulate the diffusion of molecules. We discuss how pattern formation within a Turing model might be influenced by the geometry of the spatial discretisation and the numerical method.

Poster Session - Board: 107 / 90

Polarity-dependent folding of epithelial cell sheets in three dimensions

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The apical-basal cell polarity endows epithelial tissues with distinct biochemical and mechanical properties at the apical, basal, and lateral sides of tissues. Mounting evidence shows that remodelling of epithelial cell polarity, where polarity regulators redistribute their locations on the cell membrane, causes changes of cell shapes that drives tissue morphogenesis during embryonic development. However, the principles underlying epithelial tissue morphology formation regulated by remodelling of intracellular polarity remain elusive. Using mathematical modelling and computer simulations, we first show how epithelial cell polarity is established, maintained, and remodelled by the interactions among the polarity regulators in the model system of fruit fly (*Drosophila melanogaster*). Then, based on a geometrical modelling for epithelial tissue deformation in three dimensions, we further demonstrate how tissue morphology is determined by its constituent cell mechanics. Finally, taking into account the polarity-dependent cell mechanics, we show that the feedback between cellular mechanics and polarity can lead to a self-organizing tissue morphogenesis in the absence of sustained external stimuli.

Poster Session - Board: 115 / 388

Simulation study to obtain biological circadian clocks that have a feature of predicting future

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Many species of animals, plants, cyanobacteria, and fungi are reported to have circadian clocks, that is, gene regulatory and biochemical network in a cell exhibiting endogenous oscillatory dynamics with a period close to 24 hours. There is diversity in the members of the circadian system, but all clocks share similar features such as temperature-compensated circadian period. Therefore, theoretical studies on a general (and abstract) network are as important as studies focusing on a specific network found in each species. Previous simulation studies using evolutionary algorithm have established a method to obtain networks that follow an autonomously oscillating dynamics. In those simulations the degree of deviation from the demanded period was defined as the cost function to be minimized by the optimization process because natural selection apparently favours a clock with a certain period, namely, 24 hours. However, if the ultimate goal is to implement the 24-hour period, it may be easier and more reliable to refer to external cues such as sunlight. Indeed, the circadian clocks are reported to have sensitivity to the light signal, and their phases are adjusted by sunlight. In addition, empirical studies have suggested that the circadian clocks play more sophisticated roles such as predicting timing of the next dawn (respectively, the next dusk) and preparing molecules required during the day (resp. during night) in advance. In the present study, we first examine the effect of sunlight as an external oscillator represented by a binary function (1 = light; 0 = dark). We compare the proportions of regulatory networks that exhibit and do not exhibit an oscillation autonomously (i.e., without the external force) among those oscillating with the same period as the external force. We also found that even the non-autonomous oscillators have an adaptive feature of the day-length compensation, showing 24-hour oscillation regardless of the proportion of the light period. Next, we introduce a novel cost function that reflects the merit of predicting future, and report shared features of networks optimized based on this cost function.

Poster Session - Board: 503 / 61

Effects of the physiological parameter evolution on the dynamics of tonic-clonic seizure

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The temporal and spectral characteristics of tonic-clonic seizures are investigated by using a neural field model of the corticothalamic system in the presence of a temporally varying connection strength between the cerebral cortex and thalamus. Increasing connection strength drives the system into 10 Hz seizure oscillations once a threshold is passed and a subcritical Hopf bifurcation occurs.

In this study, the spectral and temporal characteristics of tonic-clonic seizures are explored as functions of the relevant properties of physiological connection strengths, such as maximum connection strength, time above threshold, and the rate at which the connection strength increases or decreases (ramp rate). Dynamical analysis shows that the seizure onset time decreases with the maximum connection strength and time above threshold, but increases with the ramp rate. Seizure offset time and duration increase with maximum connection strength, time above threshold, and rate of change. Spectral analysis reveals that the power of nonlinear harmonics and the duration of the oscillations increase as the maximum connection strength and the time above threshold increase. A secondary limit cycle, termed a saddle cycle in previous studies, is also seen in this study. A detailed analysis of the saddle cycle oscillations shows that these oscillations become more prominent and robust with maximum connection strength and rate of change of the ramp. However, for a small ramp rate, the system does not exhibit any saddle cycle oscillations. We also find that if the time above the threshold is too small and the ramp rate is too large, the system does not reach to the larger limit cycle attractor of 10 Hz oscillation, and only exhibits the saddle cycle oscillations. It is also seen that the times to reach the saturated large amplitude limit-cycle seizure oscillation from both the instability threshold and from the end of the saddle cycle oscillations are inversely proportional to the square root of the ramp rate, as is the time to reach the seizure offset from the bifurcation from the saturated limit cycle oscillations.

Poster Session - Board: 254 / 247

Mathematical model for the effects of A β on calcium signalling

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Alzheimer's disease (AD) is a devastating illness affecting over 40 million people globally. The accumulation of AD associated Amyloid beta (A β) oligomers can trigger aberrant intracellular calcium signals by disrupting calcium regulatory mechanism within neurons. These disruptions can cause changes in homeostasis levels that can have detrimental effects on cell function and survival. Although studies have shown that A β can interfere with various calcium fluxes, the complexity of these interactions remains elusive. In order to better understand the impact of A β on calcium dynamics, we use a mathematical model to simulate calcium patterns under the influence of A β . More specifically, we assume that A β affects individual flux contributions through inositol triphosphate receptors, ryanodine receptors, and the plasma membrane. We show that the inclusion of A β can increase regions of mixed-mode oscillations leading to aberrant signals under various conditions. We use single and double parameter bifurcation structures to predict model solutions for various levels

of Aβ. We further demonstrate that controlling certain biophysically relevant parameters can help control aberrant signalling. These results can be used to suggest possible targets for establishing therapeutic strategies in AD pathology.

Poster Session - Board: 306 / 355

Predicting ecosystem responses to species eradications and reintroductions: an uncertain future?

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Species eradications and reintroductions are drastic management actions that alter ecosystem structure with the end goal of conserving or restoring one or more species of interest. Because of the complexity of ecosystem food webs, these actions can have unintended consequences on other parts of the ecosystem. Even with the best available data, predicting future trajectories of the ecosystem with high precision is not always possible. In this talk, I demonstrate the situations where ordinary differential equation (ODE) models of the ecosystem food web, calibrated to species abundance data, can or cannot be used to accurately predict future responses of the ecosystem to species eradications and/or reintroductions.

Poster Session - Board: 603 / 165

Sex differences in hepatic one-carbon metabolism

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There are large differences between men and women of child-bearing age in the expression level of 5 key enzymes in one-carbon metabolism almost certainly caused by the sex hormones. These male-female differences in one-carbon metabolism are greatly accentuated in during pregnancy. Thus, understanding the origin and consequences of sex differences in one-carbon metabolism is important for precision medicine.

We have created a mathematical model of hepatic one-carbon metabolism, based on the underlying physiology and biochemistry. We use the model to investigate the consequences of sex differences in gene expression. We use the model to give a mechanistic understanding of observed concentration differences in one-carbon metabolism and explain why women have lower S-adenosylmethionine, lower homocysteine, and higher choline and betaine. We give a new explanation of the well known phenomenon that folate supplementation lowers homocysteine and we show how to use the model to investigate the effects of vitamin deficiencies, gene polymorphisms, and nutrient input changes.

Our model of hepatic one-carbon metabolism is a useful platform for investigating the mechanistic reasons that underlie known associations between metabolites. In particular, we explain how gene expression differences lead to metabolic differences between males and females.

Poster Session - Board: 213 / 337

Single cohort vaccination can be cost-effective. Paradox in HPV mitigation model for Moldova.

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Human papillomavirus, or HPV, is a sexually transmissible virus infection, which is necessary risk factor for developing cervical cancer, most common type of cancer in working age women in Moldova. We observe both behavioural change (increase in sexual partner acquisition rates) and demographical change (population ageing and massive emigration, but still very young), which both corresponding to second demographic transition since Soviet Union collapse (yearly expenditure on health limited to 150 EUR-per-capita). Moldova will spend around 400,000 EUR on 'single cohort' vaccination in 2018, which cost effectiveness is questionable, because vaccinating a single cohort may not have a substantial effect in other countries. Thus we examine such a single vaccination scenario to show its conditional cost-effectiveness.

We have run computer simulation to prepare cost-benefit/effectiveness analysis for different vaccination strategies, various screening programs and preventive programs for Moldova in low resource settings, based on its own demography and sexual behaviour. We used data since 1998 to 2017 to adjust model parameter and we project till around 2038. Model aggregated the most important paths of infection, cancer development, uncertainty in healthcare capacity and sexuality and prevention scenarios with around 100 differential equations (stochasticity introduced in sexual partner change rates).

Single cohort vaccination could be both cost-beneficial (total cost reduction balance intervention cost before 2037) and cost-effective (with incremental impact in 20 years perspective on the level of 2300 EUR/QALY).

The possible explanation of this nonintuitive behaviour is transitional situation in Moldova ($R_0 \sim 1$), still small change of conditions could cause strong effect in epidemiology. Main effect of intervention is via men, which avoid infection and will not infect other women. This can have effect probably while changing partners is still not as common as in other countries. However, even slight change in initial conditions and parameter values could diminish positive effect (e.g. faster partner acquisition rate increase).

Poster Session - Board: 405 / 408

Can we future-proof phylogenetic consensus trees?

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Consensus methods are widely used for combining phylogenetic trees into a single estimate of the evolutionary tree for a group of species. But how robust are these methods to future information? If additional species are added to the original set of trees, will the expanded consensus tree simply

be an expansion of the original consensus tree? In this talk I will formalise and answer this question. Joint work with David Bryant (Otago, NZ) and Mike Steel (Canterbury, NZ).

Poster Session - Board: 610 / 524

Network inference of circadian clock

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The mammalian circadian rhythm is governed by the principal clock which is located in the suprachiasmatic nucleus (SCN). This clock is composed of tens of thousands of neurons and their connection to one another is essential to important roles of SCN: synchronization, entrainment to light, etc. Previous studies about the SCN network used the maximal information coefficient (MIC) statistic to oscillating time course data during resynchronization after desynchronization by TTX. Since this method requires desynchronization and resynchronization, it takes a long time and the recovered structure may not be similar to the normal SCN network. Finally, even though numerous studies argued that the connection between SCN cells are asymmetric, MIC cannot detect directionality.

We develop our own method, which can detect causality. This method does not require desynchronization by TTX, so it takes shorter time and one can obtain the normal network structure of the SCN. Moreover, it is able to obtain main results of previous studies: small-world network, exponential distribution of node degree. Finally, as our method can diagnose causality, our method can also be used to verify the asymmetry of the SCN.

Predator-prey, competition, extinction / 266

A prey-predator model with gestation period

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In this talk, we consider the dynamics of a Lotka-Volterra prey-predator model by a class of delay differential equations. The number of prey varies due to a general nonlinear predators' consumption rate with delays. Under the assumption that the consumption rate is monotonically increasing with respect to the number of prey, we investigate the effect of the nonlinearity and delays on the asymptotic behaviour of the model. For the case where the consumption rate is described not only as Holling type I,II but also as Holling type III, some ongoing studies are also introduced. Comparison for the assumptions on the incidence rates appearing in prey-predator models with those in epidemiological models, will be also discussed.

Predator-prey, competition, extinction / 411

Bayesian modelling on the expected extinction time of species.

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In this study, we propose a new Bayesian approach to calculate the expected extinction time of a species based on historical sighting record data. Unlike other work, our model allows comprehensively for uncertainties, provides the expected extinction time and the probability of extinction. It is extremely difficult to determine whether a species is extinct based on historical sighting records because knowing whether the last surviving individual of a species has finally died, or is just unobserved, remains problematical. Moreover, an incorrect classification of a species as extinct can lead to failure in conserving a threatened species. On the other hand, it is also undesirable to classify a species as extant when it is actually extinct as it can lead to misallocation of funds. Sightings with uncertain validity (uncertain sightings) play an important role in the inferences made and need to be taken into account better than they have been. Recent studies have considered uncertain sightings while making inferences about extinction; however, the difficulty of the problem requires making a number of limiting assumptions that significantly reduce realism. We have attempted to derive a more general model by incorporating sighting validity into a new Bayesian model development. We employ the underlying idea of the beta-geometric/beta-binomial (BG/BB) model to build our Bayesian approach for the analysis of extinction. Using the likelihood for the sighting data, along with the prior distributions of sighting probability and extinction probability, we calculate the expected extinction time using a Markov Chain Monte Carlo (MCMC) method which we simulate with JAGS. We apply this new approach to the sighting records of Caribbean monk seal (CMS), Dodo and Ivory-Billed Woodpecker species. Unlike other approaches that consider uncertainties in the sightings, our model gives Bayesian confidence intervals for the expected extinction time of a species.

Predator-prey, competition, extinction / 413

Optimal monitoring and decision support for the end of an eradication campaign

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Introduced species are a critical threat to Australian ecosystems and species. Particularly noxious examples include the European carp, feral cats, and a variety of weeds. A central aspect of introduced species management is eradication – if they can be completely removed from a region, the impact can be nullified. A central problem population eradications is knowing whether the species has been successfully removed or not. We develop a framework to model populations through time, explicitly accounting for imperfect detection and unknown detection probability. We use changing detection rates throughout a removal project to calibrate the model, which provides a quantitative method to trigger the end of a project. While invasive species are often the focus of removal efforts, they can also occur to prevent disease spread in an endangered species. I will describe how we applied this method to a Tasmanian devil depopulation, which enabled the establishment of a Tasmanian devil facial tumour disease population on Forestier Peninsular, Tasmania.

Predator-prey, competition, extinction / 396

Individual based modelling of the effects of cannibalism on genetic resistance to Bt in the fall armyworm

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The fall armyworm (*Spodoptera frugiperda*) is a pest insect which has the propensity to destroy a wide variety of common crops. It ranges over Eastern and Central North America and, since 2016, has been invasive in Africa resulting in significant economic damage. The fall armyworm is susceptible to Bt derived insecticides, making Bt modified crops a viable method for controlling this species. However, there is evidence to suggest that there is a small subpopulation of the fall armyworm which is resistant to Bt. This population remains relatively small in the wild due to the cost of resistance, which is partially mediated by the aggressive cannibalism exhibited by the larvae, since resistant larvae grow at a slower rate. Thus it may be possible to control the rise of resistance to Bt in a fall armyworm population via the creation of refuges for the nonresistant larvae who will in turn cannibalize the resistant larvae.

Here we use an individual base modelling (IBM) approach to model an infestation of fall armyworms, which models every individual's entire life cycle including cannibalistic encounters and the effects of its Bt resistance genotype. First, we explore the best underlying mathematical models to describe the individual insects in the IBM. Then we examine the problem of controlling the accumulation of resistance to Bt via adjustments to the size and spacial layout of the refuge while limiting the damage to the effected crops.

Predator-prey, competition, extinction / 296

Inequality in resource allocation among individuals and population dynamics models

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The Hassell equation is a classic discrete-time population model which has been widely used to model population dynamics of species with seasonal reproduction. This equation is a generalization of the Beverton-Holt equation with an additional exponent, and can describe various types of reproduction curves exhibiting from exact-compensation (contest competition) to over-compensation (scramble competition) depending on the value of the exponent. The value of the exponent and the resulting density dependence is thought to be related to the degree of inequality in resource allocation among individuals; contest curves result from unequal resource allocation, and scramble curves, from equal allocation. However, as the model is a phenomenological one at the population level, this relation between the exponent and the inequality in resource allocation has mostly been discussed only phenomenologically. Although some authors have actually derived the Hassell equation from first-principles by considering specific competition models among individuals, the exponent of the derived models does not match the naive expectation above. This study explores whether it is possible to derive from first-principles such a Hassell model that its exponent is related to the inequality in resource allocation by considering resource competition among individuals. I demonstrate that such a Hassell model can indeed be derived by assuming that each individual obtains a constant amount of resources (a resource unit) at a time, and that the competition for such a discrete resource unit among individuals is repeated many times. Different sizes of the resource unit generate different degrees of inequality, and the exponent of the derived model turns out to depend on that size, thus being related to the degree of the inequality. The derived model reduces to the Beverton-Holt

model when the inequality is highest, and to the Ricker model when the inequality is lowest. Finally, I discuss how replacing an assumption on fecundity with more realistic one changes the functional form of the derived model, and the extension to two-species competition models as well.

Predator-prey, competition, extinction / 221

Predation or frequency dependence, which of them controls dimorphism oscillations in prey predator system?

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Oscillation of lateral asymmetry dimorphism is first found in scale eating cichlid, *Perrisodus microlepis*. Fraction of their lefty morph oscillates around 0.5 in about 5 year period. Other fish or aquatic invertebrates also reveal lateral asymmetry dimorphism and oscillation of morph fractions. One of key factors of oscillation is cross predation dominance: lefty predator eats more righty prey than lefty prey, and vice versa. When lefty is major in predator, righty prey decrease, then larger fraction of lefty prey increases righty predator, and so on. This cycle appears to lead to the laterality oscillation. However the story is not such simple. A simple ODE model of prey predator system with cross predation dominance has no limit cycles, its coexisting equilibrium is stable, though almost neutral. Introduction of time delays due to growth periods destabilizes the coexisting equilibrium and leads to a limit cycle of oscillating dimorphism fraction. However, this laterality dimorphism oscillation due to time delays of growth periods and predation cycle can not explain that observed in fields. Amplitude and period of fraction oscillation are almost 1.0 and 50 ~ 250 years in the model, while they are 0.1 ~ 0.3 and 3 ~ 6 years in fields. Another factor of oscillation in morph fraction is frequency dependence. When lefty scale eaters are more common, righties eat more scales and have higher reproductive success. We introduce frequency dependent predation success into the model: rarer predator eats more prey. This frequency dependence, however, ends up with the vanish of oscillation by either stabilization of coexisting equilibrium, or fixation one laterality morph. Another frequency dependence, that of prey selection, i.e. predator eats more common prey morph, stabilizes coexisting equilibrium. The model with both of frequency dependence finally shows oscillations with realistic amplitudes and periods. We conclude that oscillation of lateral asymmetry morphs is caused not by predation cycle, but by frequency dependence in both of prey and predator, i.e. rarer predator or prey morph is advantageous and become common after a few years.

Reaction networks & stochasticity / 98

Variance reduction approaches to efficient simulation of biochemical reaction network models

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The complexity of biochemical reaction networks means that we often rely on stochastic simulation to investigate their potential behaviours, generating multiple sample paths from the model and using them to estimate summary statistics of interest. However, for realistic models, existing Monte Carlo

methods are often prohibitive when it comes to exploring the range of possible model behaviours, conducting parameter sensitivity analysis, or parameter inference and model selection.

One approach that has the potential to mitigate these issues is that of variance reduction. Instead of attempting to reduce the computational cost of generating individual sample paths, we instead aim to reduce the variability in the summary statistics we are interested in. Computational savings can then be made because fewer sample paths are required to generate estimates to within a specified error. In this talk I will describe variance reduction approaches biochemical reaction network models. I will first show how point estimates can be generated simply and efficiently, and then outline how extensions to the basic method allow variance reduction approaches to be applied to a range of problems and summary statistics.

Reaction networks & stochasticity / 16

Reflected diffusions and (bio)chemical reaction networks

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Continuous-time Markov chain models are often used to describe the stochastic dynamics of networks of reacting chemical species, especially in the growing field of systems biology. Discrete-event stochastic simulation of these models rapidly becomes computationally intensive. Consequently, more tractable diffusion approximations are commonly used in numerical computation, even for modest-sized networks. However, existing approximations (e.g., linear noise and Langevin), do not respect the constraint that chemical concentrations are never negative.

In this talk, we propose an approximation for such Markov chains, via reflected diffusion processes, that respects the fact that concentrations of chemical species are non-negative. This fixes a difficulty with Langevin approximations that they are frequently only valid until the boundary of the positive orthant is reached. Our approximation has the added advantage that it can be written down immediately from the chemical reactions. Some numerical examples illustrate the advantages of our approximation over direct simulation of the Markov chain or use of the linear noise approximation.

This talk is based on joint work with Saul Leite, David Anderson and Des Higham.

Reaction networks & stochasticity / 100

Efficient adaptive uniformisation for the analysis of biochemical reaction networks

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A common modelling technique to include stochastic effects in biochemical reaction networks is the use of discrete-state continuous time Markov chains. Analytic results for the resulting systems are rare and one often has to rely on stochastic simulation approaches to quantitatively probe their dynamics. Many conventional simulation methods, however, become prohibitively slow if the system is characterised by multiple different time scales, i.e. for stiff systems.

In this contribution we consider the application of adaptive uniformisation techniques which can significantly reduce the number of simulation trajectories needed to estimate summary statistics of the reaction network. By making the uniformisation rate adaptive, rather than fixed, this method can efficiently deal with multiple scales in the dynamics of reaction networks.

Recent perspectives on mathematical epidemiology / 177

What is the likely impact of group A *Streptococcus* vaccines on throat and skin infections across different populations?

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Severe diseases arising as sequelae of superficial skin and throat infections with group A *Streptococcus* (GAS) are important causes of morbidity and mortality worldwide. The observed high level of heterogeneity in GAS prevalence across various temporal and spatial settings suggests potentially complex dynamics of population transmission. One of the most visible indicators of heterogeneity is the different prevalence of skin and throat infections across populations.

Sustained control of GAS infections in settings of poverty has failed, and an effective vaccine may be the most practical long-term strategy to reduce the burden of GAS-related disease. Research into GAS vaccines has been ongoing for many decades, and there are a number of vaccine candidates currently at various stages of development. Those based on the M-protein, the major virulence factor of GAS, include multivalent vaccines targeting the variable N-terminal of the M-protein, and vaccines that contain antigens from the conserved C-repeat region. It is anticipated that these vaccines will provide varying levels of protection across populations depending on the match between circulating and vaccine strains.

We have developed a compartmental model of GAS transmission incorporating skin and throat infection separately and allowing for interaction between the two. To address the many uncertainties that exist around GAS transmission and immunity, we used the Metropolis-Hastings algorithm with informative priors to sample parameter space and simulate our model. We conducted three separate explorations to match epidemiologic attributes observed in population settings with different combinations of skin and throat infection prevalence: 1) throat < 10%, skin 30–60%; and 2) throat 5–20%, skin 5–10%; and 3) throat 5–20%, skin 30–60%; where throat infections may be either symptomatic or asymptomatic.

Early analysis of parameter distributions capable of producing these different combinations of skin and throat infection prevalence has shown interesting patterns for further investigation. While some model parameters are similar across the population settings, others such as the duration of infection, show strong tendencies for differences between populations. We are in the process of considering the plausibility of parameter variation across population settings, which may be driven by clinical, molecular and behavioural characteristics. Once we have ascertained the robustness of our parameter distributions, we will simulate vaccination in the model. To represent the variation in mechanism of vaccine candidates currently under development, we will allow for vaccines to act in different ways in the model, such as having reduced impact on skin infection compared to throat

infection. We will use the model to determine the importance of the vaccine mechanism in driving likely impact across population settings.

Recent perspectives on mathematical epidemiology / 280

Modelling the renal disease epidemic among HIV-infected individuals

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The number of HIV+ individuals who develop end stage renal disease (ESRD) and require life-long dialysis treatment has been continually rising in some regions around the world. A differential equation-based mathematical model was developed to assess the impact of antiretroviral therapy on the progression to disease and to project the future prevalence of HIV+ ESRD. The goals of this study are to parameterize the model with new data on the populations of individuals with HIV/AIDS and those with HIV+ ESRD, and to extend the model to take into account greater complexity in the population dynamics. We also expand the model's analysis to predict treatment recommendations for the population of HIV+ individuals at risk for developing renal disease. Further studies will use the model to estimate how much the development of renal disease and treatment levels have changed over time, and to predict the treatment levels needed to slow the increase of this epidemic.

Recent perspectives on mathematical epidemiology / 47

Comparing malaria surveillance with periodic spraying in the presence of insecticide-resistant mosquitoes: Should we spray regularly or based on human infections?

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There is an urgent need for more understanding of the effects of surveillance on malaria control. Indoor residual spraying has had beneficial effects on global malaria reduction, but resistance to the insecticide poses a threat to eradication. We develop a model of impulsive differential equations to account for a resistant strain of mosquitoes that is entirely immune to the insecticide. The impulse is triggered either due to periodic spraying or when a critical number of malaria cases are detected. For small mutation rates, the mosquito-only submodel exhibits either a single mutant-only equilibrium, a mutant-only equilibrium and a single coexistence equilibrium, or a mutant-only equilibrium and a pair of coexistence equilibria. Bistability is a likely outcome, while the effect of impulses is to introduce a saddle-node bifurcation, resulting in persistence of malaria in the form of impulsive periodic orbits. If certain parameters are small, triggering the insecticide based on number of malaria cases is asymptotically equivalent to spraying periodically.

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Target product profiles for second-generation childhood malaria vaccines

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Clinical trials of the four-dose RTS,S/AS01 vaccine for *P. falciparum* malaria demonstrated a protective effect in young children and, beginning in 2018, the vaccine will be evaluated through a large-scale pilot implementation program in Ghana, Kenya and Malawi. Recent evidence from a phase 2a challenge study indicates that varying the timing and amount of the fourth dose could further improve the public health impact.

We used a dynamic modelling approach to inform target product profiles (TPPs) for a second-generation malaria vaccine, focussing on the vaccine properties of initial efficacy, duration of protection, dosing schedules and coverage. We simulated the changing anti-circumsporozoite antibody titre following vaccination, related titre to vaccine efficacy, and then implemented this efficacy profile within an individual-based model of malaria transmission. We developed a range of efficacy profiles for different vaccine schedules and used these to evaluate the relative impact of initial efficacy, duration, and fourth dose characteristics. We ran the simulations across a range of epidemiological strata, measuring clinical cases averted children younger than five years.

We found that in the first decade of delivery, a vaccine with high initial efficacy vaccine resulted in more clinical cases averted, compared to a longer duration vaccine, and that the effect was more pronounced in high malaria prevalence settings. However, the low initial efficacy and long duration schedule averted more cases across all age cohorts if a longer time horizon was considered. We also observed that a higher antibody titre resulting from the fourth dose was always advantageous, and that a longer delay between doses three and four averted more cases in older age classes.

Our results indicate that an imperfect malaria vaccine, initial efficacy may be more important than vaccine duration. An optimised malaria vaccine may outperform the current RTS,S, but timing of the fourth dose determines the age group that benefits most. This TPP analysis could provide insight for vaccine developers and policy-makers into how distinct characteristics of a malaria vaccine may translate to public health outcomes.

Recent perspectives on mathematical epidemiology / 424

Climate change and the equine infectious anemia virus epidemic

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Equine Infectious Anemia Virus (EIAV), a retrovirus that establishes a persistent lifelong infection in horses and ponies, and which can be transmitted by vectors (biting flies), is endemic in regions with warm climates. With the advent of global warming, research have shown that vector-borne diseases may be on the rise. This study seeks to understand how climate change will affect the EIAV epidemic, especially in endemic regions. We developed two vector-host mathematical epidemic models of EIAV infection that describe the direct transmission of EIAV between wild and domestic horses, and also through vectors: a basic model and a patch model. The models are rigorously analysed

mathematically. The effects of variability in the model parameters are also investigated. Results of disease thresholds give conditions necessary for the control of the infection. We hypothesise that climate change to warmer temperatures may increase the time that the virus can thrive in the vector. Model results, which are underway, could be significant for the control of any or all fly-borne pathogens.

Recent progress in evolutionary theory: Coevolution, diversity, and networks / 360

Predicting vegetation diversity & structure from ecological and evolutionary first principles

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Walking through any forest, one is struck by the variety of plant forms coexisting. To explain vegetation structure and diversity, models must allow for multiple species to coexist, and ultimately, predict the outcome of community assembly in different environments. In this talk, I describe how adaptive dynamics theory provides a new framework for predicting the mixtures of species traits that are favoured in vegetation. Predictions are generated by embedding trait-based coexistence and selection into models of forest dynamics, mapping from physiological trade-offs in plant function to individual-level outcomes such as growth rates, and ultimately population-level demographics, and fitness. Results thus far show how i) how key trait-based trade-offs enable different strategies to coexist via successional niche differentiation; ii) how joint consideration of multiple traits can produce forests of higher diversity than was previously thought possible, and iii) how trait mixtures respond to environmental conditions. To conclude, I consider some major challenges in applying this approach to making large-scale predictions of forest structure.

Recent progress in evolutionary theory: Coevolution, diversity, and networks / 445

Modelling eco-evolutionary dynamics: an integrative overview

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Analyzing humankind's interactions with our collective environment typically requires understanding eco-evolutionary dynamics in complex adaptive systems. This is especially important for mitigating anthropogenic impacts on the biosphere, managing the multifaceted services provided by ecosystems, and shaping social interactions among agents utilizing these systems. Understanding complex adaptive systems requires a marriage of ecological dynamics with evolutionary dynamics. This is because adaptations in living systems cannot be understood without accounting for the rich ecological and social embedding of populations and communities; conversely, predicting the future of ecosystems, especially when exposed to strong anthropogenic impacts, necessitates accounting for the prospect of rapid evolution, both biological and cultural. Bridging the often still profound gap between theories and applications, this presentation provides an integrative overview of modern modelling approaches linking ecological and evolutionary dynamics in real-world complex adaptive systems.

Recent progress in evolutionary theory: Coevolution, diversity, and networks / 389

Mutualistic network maximizing species abundance under exploitative competition

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The abundance of a pollinator species can be affected by other pollinators sharing the nutrients from the same plants. Such an exploitative competition between the animal species may affect the species abundance the network structure of plant-pollinator mutualistic communities, which remains to be understood. Here we study a model of the mutualistic network evolution towards increasing the species abundance with the exploitative competition between pollinators and mutualism in the abundance dynamics. We show that hub plants having many pollinators are very rare while a few super-hub pollinators appear with the generalized interaction, contrasted to equally many hubs of both types without the exploitative competition. More interestingly, it turns out that the abundance of plant species increases slightly with increasing the exploitative competition strength. To understand the origin of this phenomenon, we obtain the inverse of the generalized interaction matrix approximated in the weak-interaction limit. The leading structural factors relevant to the species abundance are identified, which are shown to be instrumental in optimizing the network structure to increase the mutualistic benefit and lower the cost of exploitative competition.

Recent progress in evolutionary theory: Coevolution, diversity, and networks / 394

Global shapes of evolutionary trees in trait spaces can be described by the Price equation

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Diversification and extinction are ubiquitously repeated in the evolutionary histories of biological communities. A minimal mechanism for driving the repeated diversification and extinction is a combination of resource competition in one trait and a weak directional selection in another trait; resource competition induces diversification in the first trait, but inevitably nonuniform innovations in the second trait among the diversified lineages induce further diversification of the most innovated lineage, excluding the other outdated ones. In this dynamics, the evolutionary speed of community average of the second trait can be partitioned into the contribution by directional evolution of each lineage consisting the community, i.e., within-lineage evolution, and the contribution by changes of those lineages' frequencies, i.e., between-lineage selection. This study generalizes such a partitioning by the Price equation for an arbitrary bivariate trait space, by which the global shapes of evolutionary trees in the trait spaces can be understood in terms of within-lineage evolution and between-lineage selection.

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Coevolution of horizontally transmitted mutualistic systems

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Mutualism based on reciprocal exchange of costly services must avoid exploitation by “free-riders”. Accordingly, hosts discriminate against free-riding symbionts in many mutualistic relationships. However, as the selective advantage of discriminators comes from the presence of variability in symbiont quality that they eliminate, discrimination and thus mutualism have been considered to be maintained with exogenous supply of free-riders. In this study, we tried to resolve the “paradoxical” coevolution of discrimination by hosts and cooperation by symbionts, by comparing two different types of discrimination: “one-shot” discrimination, where a host does not reacquire new symbionts after evicting free-riders, and “resampling” discrimination, where a host does from the environment. Our study shows that this apparently minor difference in discrimination types leads to qualitatively different evolutionary outcomes. First, although it has been usually considered that the benefit of discriminators is derived from the variability of symbiont quality, the benefit of a certain type of discriminators (e.g. one-shot discrimination) is proportional to the frequency of free-riders, which is in stark contrast to the case of resampling discrimination. As a result, one-shot discriminators can invade the free-rider/non-discriminator population, even if standing variation for symbiont quality is absent. Second, our one-shot discriminators can also be maintained without exogenous supply of free-riders and hence is free from the paradox of discrimination. Therefore, our result indicates that the paradox is not a common feature of evolution of discrimination but is a problem of specific types of discrimination.

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R_0 centrality in metapopulation networks: finding the epidemiological and evolutionary hotspots

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Identifying the epidemiological key-stone communities in a metapopulation network is primarily important in designing efficient control against an infectious disease. Various network centrality measures commonly utilized for this purpose haven't directly focused on the most important measure in epidemiology: the basic reproductive number, R_0 , of epidemiological dynamics on the network, which determines whether or not the infectious disease spreads over the whole network. We here introduce a new centrality measure, R_0 -centrality, which quantifies how sensitive is the control in each local community to the reduction in R_0 of the whole network. Our perturbation analysis then reveals that the largest local population in the network should have extremely large R_0 centrality than the others, indicating that all the effort in control should be directed to the largest community. For example, when applied to the commuter network of the Tokyo metropolitan area, we found that the impact of control at the largest daytime-population, that around Shinjuku station, is more than 1,000 times stronger than that at the second largest daytime-population, that around Tokyo station, even though the difference between population sizes are only 1.5 times between them.

Once an infectious disease has already spread over the network, we found that the opposite extreme control becomes optimum: indeed, to reduce the total number hosts that have ever exposed to the infectious disease after it has already penetrated in the network, the optimal policy is to spreading controls shallowly and widely over the network. We also discuss the conditions under which “treating-only-the-biggest” control becomes the optimum, and the key-stone community for the emergence is virulent or resistant pathogens.

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Estimating the basic reproduction number at the beginning of an outbreak**Authors:** Sawitree Boonpatcharanon¹ ; Jane Heffernan¹ ; Hanna Jankowski¹¹ York University**Corresponding Author:** sawitree.boonpat@gmail.com

The basic reproduction number, R_0 , is a key quantity allowing public health officials to track how quickly an outbreak spreads through a population. In this talk, we compare several different estimators of R_0 assuming that only weekly data is available, with a focus on the early stages of an outbreak. We compare four estimators: a variant on maximum likelihood, incidence decay, incidence decay with exponential adjustment, and partially observed Markov process approaches. Our simulations concentrate on a flu epidemic, and several different scenarios are considered. In particular, we study also the setting of model misspecification, when one model structure is fit to data generated by a different model. Benefits and drawbacks of each R_0 estimator will be discussed.

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Meta-population modelling to evaluate vaccination policy alternatives vis-à-vis measles and rubella in China**Author:** John Glasser¹**Co-authors:** Huaqing Wang² ; Lixin Hao² ; Qiru Su² ; Chao Ma² ; Zhilan Feng³ ; Lance Rodewald⁴¹ Centers for Disease Control and Prevention² China CDC³ Purdue University⁴ WHO China**Corresponding Author:** jglasser@cdc.gov

Background: Measles and rubella are rash illnesses that typically afflicted young children in the pre-vaccination era, but rubella usually is mild while measles may be severe. Because child deaths to which measles contributes often have other proximate causes, measles mortality is under-ascertained. Rubella during the first trimester invariably causes miscarriages, stillbirths and, among livebirths, congenital rubella syndrome (CRS), an array of individually severe afflictions that often co-occur. As childhood vaccines commonly include antigens to the viruses causing both diseases, vaccination programs must be designed to attain disparate goals: prevent measles among young children and rubella among young women. By virtue of increasingly effective routine vaccination, together with targeted supplemental immunization activities (SIAs), health authorities in the People's Republic of China have reduced measles' reproduction number from about 18 to 2.3. Despite substantial residual susceptibility among young adults, more in some province-level jurisdictions than others, sustained childhood immunization likely would eliminate measles eventually. Because routine vaccination against rubella began more recently, residual susceptibility is concentrated among adolescents. Nonetheless, childhood immunization has reduced rubella's reproduction number from 7.6 to 1.2. To support global eradication efforts, as well as expedite morbidity and mortality reductions in China, we evaluated alternative SIAs via mechanistic mathematical modelling.

Methods: Our model Chinese population is stratified by immune status (susceptible to infection; infected, but not yet infectious; infectious; and recovered or immunized), age (0, 1-4, 5-9, ..., 65+ years), and location (31 provinces, municipalities or administrative regions). It includes a function by which contacts between members of different groups are a mixture of preferential and proportionate with

respect to age, but decline exponentially with distance at age-dependent rates. We estimated initial conditions and most parameters from recent cross-sectional serological surveys, disease surveillance and demographic observations. Then we evaluated the effective reproduction numbers and their partial derivatives with respect to sub-population immunization rates. Within regions, these gradients identify province-level jurisdictions where vaccination would reduce the effective reproduction number the most. And within jurisdictions, they identify age classes where vaccination would be most effective. We corroborated our analytical results by simulating adolescent and young adult SIAs using a deterministic model with seasonally-forced person-to-person contact rates. And, using a demographically-realistic stochastic model of a relatively small but representative population, we estimated the risk of rubella outbreaks, burden of CRS, and impact of adolescent vaccination.

Findings: Measles' gradients are more heterogeneous than rubella's, but generally indicate that vaccinating young adults is the optimal strategy. Simulations corroborate this, but indicate that a catch-up campaign among adolescent schoolchildren would accelerate elimination nonetheless, with timing dependent on uptake. Moreover, this strategy is optimal for rubella, which is woefully under-reported, especially among adults. Thus, using measles-rubella or measles-mumps-rubella vaccine in SIAs during the first months of several consecutive school years would both accelerate measles elimination and avert impending outbreaks of rubella that, because of the immune profile in China, would greatly increase the incidence of CRS. Interpretation: These results are largely due to indirect effects (i.e., fewer infections than vaccinated people might otherwise cause), which meta-population models with realistic mixing are uniquely capable of reproducing accurately.

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Modelling of the Spread of MERS-CoV

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Middle East Respiratory Syndrome Coronavirus (MERS-CoV) has been persistent in the Middle East region since 2012. Abundant scientific evidence showed that dromedary camels are the primary host of the virus. Majority of human cases (i.e. 75% or 88%) are due to human-to-human transmission, while the others are due to camel-to-human transmission. Mathematical modelling of MERS-CoV camel-to-camel transmission was lacking. Using the plug-and-play likelihood-based inference framework, we fitted a susceptible-exposed-infectious-recovered-susceptible model of camels to the reported human cases with a constant proportion of human cases from camels (i.e. either 25% or 12%). We considered two scenarios: (i) the transmission rate among camels is time-varying with a constant spill-over rate from camels to human, or (ii) the spill-over rate is time-varying with a constant transmission rate among camels. Our estimated loss-of-immunity rate and prevalence of MERS-CoV infections among camels largely matched previous serological or virological studies, shedding light on this issue. We recommended including dromedary camels in animal surveillance and control of MERS-CoV in Saudi Arabia which could help reduce their sporadic introductions to humans.

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Ecological stability, epidemiological stability and reservoirs of infection

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The structure of an ecosystem and the interaction of the species within it can determine whether a pathogen can persist. We have described a model for interacting species that are hosts and non-hosts of a pathogen. The population densities of the ecosystem species can determine the value of the basic reproduction number, \mathcal{R}_0 . We have defined concepts of ecological and epidemiological stability, shown how changes in the ecosystem can change the dynamics of the pathogen, and how the introduction or removal of a pathogen can lead to changes in the ecosystem structure. In particular, the so-called dilution effect, where an increase in biodiversity leads to a reduction in the prevalence of an infectious disease, has been the subject of speculation and controversy. We have found criteria for when the dilution effect is present, or when the opposite (amplification) effect may occur. Another concept often used informally in the literature is that of a reservoir of infection. Finding a robust definition of a reservoir is not straightforward, particularly as the presence of other species in an ecosystem, even non-host species, can change the value of \mathcal{R}_0 .

Collaborative research with Hans Heesterbeek.

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Corrections to predictions of the basic reproduction number

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The basic reproduction number, R_0 , derived from ordinary differential equation models is a powerful predictor of the severity of an infection and can help inform prevention and mitigation strategies. Many of the parameters used in ODE models are mean values of time-dependent distributions. Here, we show how we can incorporate properties of these distributions to refine estimates of R_0 for a series of ubiquitous models used in epidemiology. These corrections are applied to the R_0 estimate as opposed to the model itself, allowing simple models to be used, and better predictions to be made post-hoc as more data becomes available. Moreover, we address some difficulties in trying to extend these corrections to more complex models.

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Inducing chondrogenesis in layered tissue engineering constructs with exogenous TGF- β

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The differentiation of mesenchymal stem cells (MSCs) into chondrocytes (native cartilage cells), or chondrogenesis, is a key step in the tissue engineering of articular cartilage. Chondrogenesis is regulated by transforming growth factor-beta (TGF- β), a short-lived cytokine whose effect is prolonged by storage in the extracellular matrix (ECM). Tissue engineering applications require the complete differentiation of an initial population of MSCs, and two common strategies used to achieve this in vitro are (1) co-culture the MSCs with chondrocytes, which constitutively produce TGF; or (2)

add exogenous TGF- β . We are motivated by recent experiments where a tissue engineering construct is seeded with cells in spatially separated layers, with a layer of MSCs lying below a layer of chondrocytes, and is then stimulated with exogenous TGF- β from above.

To investigate the efficacy of this seeding strategy we develop a reaction-diffusion model for the interactions between the TGF- β , MSCs and chondrocytes. A feature of this model is that it describes the different forms TGF- β takes throughout its lifecycle, some of which are bound to the ECM (and so not diffusible), and the process by which the TGF- β cytokine is cleaved from the molecular latency complex it is secreted with to become available to cell receptors. Using this model we demonstrate that the concentration of TGF- β required to induce chondrogenesis of the MSCs in the lower layer is not physically realistic for layers of equal depth (as used experimentally). We then suggest improvements to the current experimental protocols, as well as compare the use of the layered cell seeding strategy with a strategy where the initial cell populations are well-mixed (which we have previously investigated with an ordinary differential equation model).

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Thin-film modelling of multiphase collagen gel mechanics

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Cells are often grown within collagen gels *in vitro* for applications in tissue engineering. The behaviour of these cells is regulated by their mechanical environment; however, the forces exerted by cells in turn affect the mechanical behaviour of the gel. We aim to better understand the interactions between the cells and the gel using mathematical modelling.

We have developed a multiphase model for this system, incorporating cells and their traction forces alongside chemical effects such as osmosis. To date, we have modelled this problem in one-dimensional Cartesian and spherical coordinates, mimicking experiments performed with spheres of collagen gel. However, these gels are often produced in Petri dishes, resulting in a thin disc. We have therefore transformed our model to examine this type of geometry. In this presentation, we will demonstrate how we can exploit thin-film approximations to reduce the two-dimensional system to a leading-order, one-dimensional model. We will also discuss the equilibrium behaviour of this reduced thin-film system.

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Stopping waves: geometric analysis of coupled bursters in an asymmetric excitation field

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Bursting is a type of electrical activity seen in many neurons and endocrine cells where episodes of action potential firing are interspersed by silent phases. Pancreatic β -cells show so-called square-wave bursting when stimulated by glucose, which causes Ca^{2+} oscillations and pulsatile insulin secretion. β -cells are electrically coupled within pancreatic islets, and excitation waves are observed to propagate through the β -cell population. When the islet is exposed to a glucose gradient, so that some cells would be active also when uncoupled while others would be below the activity threshold

and thus silent, Ca^{2+} waves propagate only partly through the islet and stop approximately where the glucose concentration is at the threshold for cellular activity. Simulations of existing mathematical models of coupled β -cells produce waves that propagate too far into the region of “silent” cells, compared to experiments, unless unrealistic model assumptions are imposed. Here, we investigate why β -cell models fail to reproduce the experimentally observed wave properties and tend to synchronize the β -cell population too easily, by using a prototypical polynomial bursting model and slow/fast bifurcation analysis. Our analyses indicate how to modify the model so that the excitation waves stop at the border between “active” and “silent” cells. We verify this property by simulations using such a modified model for a chain, and for a cubic cluster, of coupled β -cells. Furthermore, we show how our one- and two-parameter bifurcation analyses allow us to predict where the simulated waves stop, for both the original model and the modified version. Our results indicate the geometrical structure that biophysical β -cell models should have to possess biologically realistic wave and synchronization properties.

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Multi-cellular modelling of cellular mechanisms gives insights on the maintenance of epidermal tissue structure

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The inter-follicular epidermis (IFE) forms the outer-most layer of the skin. Many individual components fundamental to healthy IFE structure are known: proliferation occurs only in a basal layer; above this layer cells differentiate into keratinocytes forming further distinct layers before they are shed from the surface. However, a definitive understanding of how the balance between proliferation, differentiation, and cell shedding is maintained in IFE tissue during homeostasis does not yet exist.

We have developed an agent-based multi-cellular computational model to simulate tissue homeostasis in the skin. Epidermal cells are represented as overlapping spheres, and cell divisions are represented as stochastic time-driven events. Cell movement is determined by adhesive attractive forces and repulsive forces between other cells and the basal membrane. The magnitude of these forces depends upon the types of the interacting bodies, and can vary depending on factors such as cell age and location.

Using this model we have analysed the impact of different cell mechanisms and behaviours on the tissue in order to investigate alternate hypotheses around maintenance of tissue structure. Results of this study provide insights into the critical mechanisms and behaviours, and will guide the future integration of detailed biochemical regulation processes.

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How feedback mechanisms shape calcium oscillations in Hepatocytes

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Variation of calcium concentration in hepatocytes (liver cells) is known to modulate diverse cellular functions, including bile secretion, glucose and energy metabolism and vesicular trafficking. A major question in the study of calcium signalling in hepatocytes is how these distinct cellular processes are controlled and organised via coordinated spatial and temporal calcium signals.

Downstream cellular responses are controlled via intracellular calcium oscillations but the underlying mechanisms which shape these oscillations have yet to be elucidated. We are interested in determining the effects of various types of calcium feedback mechanisms such as calcium feedback on Phospholipase C (PLC) and the calcium-mediated protein kinase C (PKC) feedback on the hormone receptor have on the whole-cell calcium signals. Recent experimental data suggests that hormone-induced calcium oscillations require positive calcium feedback on PLC to generate inositol trisphosphate oscillations, yielding cross-coupling between calcium and inositol trisphosphate. Furthermore, it appears that there is also a negative feedback pathway, cross-coupling PLC activation to PKC, which serves to terminate calcium spikes.

This talk will discuss recent progress in construction and analysis of a model of calcium oscillations that incorporates the new experimental results about likely feedback mechanisms in hepatocytes.

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Calcium signalling in the sperm head

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Calcium signalling is a ubiquitous mechanism that many cell types use to control a plethora of biological processes. In particular, calcium plays a large role in fertility both for egg and sperm cells. In this presentation, we will focus on the acrosome reaction, which is a calcium-modulated vesicle release that must occur for sperm to successfully fertilize the egg. We will discuss the important biological components in this reaction and develop a mathematical model that highlights how multiple pathways interact to drive this unique calcium-driven event.

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Industrial bees: when agricultural intensification doesn't impact disease burden

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The intensification of farming indisputably changes the ecology of agricultural infectious diseases with modern management practice impacting both host density and between-host contacts. We typically assert that these changes result in higher disease burdens, but there is relatively little specific modelling testing this idea. For example, the industrialisation of apiculture has been suggested to play a critical role in the increased losses of *Apis mellifera* colonies to infectious diseases, with specific apicultural practices (reflecting industry-wide intensification) implicated in higher disease burdens. Here we build multi- honeybee colony models to examine how 'apicultural intensification' in its most plausibly extreme case is predicted to impact honeybee pathogen epidemiology within apiary. Counter to the prevailing view, our models predict that intensification, captured through increased population sizes, changes in population network structure, and increased between-colony

transmission, has little effect on disease burden across an apiary. Disease burdens, and therefore impacts of intensification, are critically determined by the R_0 (reproductive ratio) of a given pathogen prior to intensification. The greatest impacts of intensification are found for diseases with initially low R_0 values, however such diseases cause little overall disease burden and so impacts are universally minor. Importantly in this context, the smallest impacts of intensification are found for diseases with high R_0 values, which appear to be typical of important honeybee diseases. Our findings highlight a lack of support for the hypothesis that current and ongoing aspects of management intensification lead to higher disease burdens in honeybees. More broadly, our work demonstrates the need for specific models of agricultural systems and management practices in order to understand the implications of management changes on disease burden.

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Explaining lazy workers in social insect colonies with evolutionary game theory

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In social insect colonies we often observe substantial levels of laziness, i.e., workers that do not engage or appear not to engage in any tasks. This is puzzling, because colonies with lazy individuals seem to be wasteful and may not be using their resources optimally. A common hypothesis is that lazy workers are a reserve workforce that can be quickly activated when rapid changes in the environment demand it.

We present an alternative explanation for laziness based on game theory. We assume that insects play a game in which they allocate their energy towards two competing tasks, foraging and temperature regulation. Both tasks need to be performed successfully for colony survival, thus the set-up reflects a coordination game.

The benefits of regulation are assumed to be concave and maximised at intermediate levels of task engagement. The benefits of foraging are assumed to be linear in effort. Benefits are shared by the whole colony, whereas costs are borne individually. Individuals learn to play this game by using social learning, and occasionally experimenting with new strategies. When experimentation is rare the population is monomorphous most of the time, and the learning trajectories of colonies can be modelled by using adaptive dynamics. Levels of laziness in the long run can be determined by studying the fixed points of the dynamics.

We find that the level of laziness crucially depends on the costs of performing the tasks. In particular, laziness can be stable under marginally increasing costs. Constant and marginally decreasing costs result in colonies without lazy individuals. Monte Carlo simulations show that our theoretical prediction is accurate under moderate levels of noise.

Our model is the first one to link specific ecological features to the puzzle of lazy workers. We discuss potential implications for empirical work and extensions of the model.

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The effect of thermoregulation on honey bee colony health and survival

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In recent years honey bee colonies have been experiencing increased loss of hives. One cause of hive loss is colony collapse disorder (CCD). Colony collapse disorder is characterised by a previously healthy hive having few or no adult bees but with food and brood still present. This occurs over several weeks. It is not known if there is an exact cause of CCD but rather it is thought to be the accumulation of multiple stressors placed on a hive. One of these stressors is the breakdown of thermoregulation inside the hive.

The bee life cycle begins with eggs that hatch into larvae that in turn pupate. The eggs, larvae and pupae together are known as brood. The hive contains combs which are made up of multiple cells; these cells house the brood. Pupal cells are capped off by adult bees (and so are known as capped brood) and they undergo changes to develop into an adult bee. In order for this capped brood to develop correctly, the temperature within the hive must be regulated by the hive bees to ensure optimal development of the capped brood. Variations in the temperature, caused by the breakdown of thermoregulation, lead to suboptimal development in adults that emerge from capped brood. In particular, their brains and flight muscles are compromised. This later leads to these bees becoming inefficient foragers which also have shorter life spans.

We model the effect of thermoregulation on hive health using a system of DDEs which gives insights into how varying hive temperatures have an effect on the survival of the colony. We show that thermoregulatory stress has the capacity to drive colony collapse disorder via a saddle-node bifurcation.

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A conceptual model for the network of potential routes of exposure of pollinators to pesticides

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A conceptual model was constructed to define the network of potential routes of exposure of pollinators to pesticides in greater detail than has previously been done. This model provides a basis for biologically and ecologically realistic basis for mathematical estimation of exposure versus time both individually and at the colony level. It also shows the distinction between primary exposure routes, such as contact during foraging with vegetation and soil, contamination of drinking water, and secondary routes of exposure in the hive including consumption of pollen, and nectar that are collected by foragers or the honey and bee bread produced in the hive. Secondary exposure from contact with nest construction materials such as wax are included. These secondary routes of exposure can affect both adults and immature life stages of social pollinators in the hive or nest. The conceptual model allows detailed consideration of the overall pattern of potential exposure, including the dynamics of exposure to various castes and life stages of social bees. This conceptual model also aids in assessing the completeness of the risk assessment and identifying exposure pathways that require further investigation.

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Division of labour in social insects: ecologies can drive modes of specialisation

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All social insects live in elaborately organised societies. Their social structures enable them to continuously manage a large set of simultaneous tasks; from scouting and foraging to colony defence, nest building, thermoregulation, and brood care. To ensure colony survival and reproduction it is vital that the colony workforce is adequately allocated to these different tasks. Social insect colonies are able to perform such task allocation with an amazing degree of flexibility, continuously adjusting to changes in environmental conditions. The resulting division of labor (DOL) is a cornerstone of all social insect societies and commonly credited as a key factor for their enormous ecological success.

The vast majority of DOL modelling has either focussed on physiological factors or on individual-based behavioural mechanisms. Comparatively little attention has been given to how social interactions regulate task allocation. None of the existing frameworks provides a direct link to integrate environmental conditions as an integral part of the modelling process (beyond task-related stimulus levels). Entomologists are now investigating specifically these factors as the keys to a better and more comprehensive understanding of workforce allocation.

We propose a new mathematical modelling framework for task allocation in social insects that directly incorporates social interactions and environmental conditions as first class elements. We use evolutionary game theory to investigate how task preferences develop during the lifetime of a colony and how DOL emerges and morphs as a result. We model the task preferences of individuals as continuous strategy choices in a simple game, in which individuals choose how to divide their efforts between different tasks. Task execution results in rewards that may be shared between colony members or go directly to the individual. The amount of reward is modulated by the collective level of investment into the task as well as by environmental factors.

Based on this framework we show that ecological conditions are a crucial determinant for the emergence of different forms of specialisation. We also find strong interactions between the prevailing learning mechanisms and colony specialisation.

Contrary to intuition we find that strong specialisation does not always relate to improved colony efficiency. Particularly, social learning appears to lead to high colony performance only in a limited range of environment types and can drive a colony into “over-specialisation” in other conditions. This suggests that social learning should only have evolved in a limited range of environments and for certain tasks. Our theoretical results thus point towards promising new directions for empirical work that can bring us a step closer to understanding how social insects achieve their outstanding ecological success.

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Modelling the force-dependent morphogenesis of fish vertebra with topology optimization

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Wolff's law states that bone morphology evolves according to their external mechanical loading. Following this law, researchers have tried to simulate bone shape formation, especially for trabecular bone, using topology optimization [1]. Less attention has been given to the bone outer shape, composed of cortical bone. However, trabecular bone and cortical bone are both mainly formed by

osteoblasts and osteoclasts. Therefore, we hypothesize that the bone outer shape also adapts to the external forces. The aim of this research is to understand the mechanism that generates the bone outer shape by reproducing the latter using topology optimization.

The fish vertebra can be divided into two parts: an inner hourglass-like structure and an outer lateral structure. Based on our observations, it turns out that numerous species present a similar hourglass-like structure but that the lateral structure strongly depends on the fish species. Lateral structures can be classified into two types. The first type exhibits a ridge structure with one or more thick plate-like bones and the second type exhibits a netlike structure in which thin plate-like bones are randomly oriented. These differences seem related to the fish motion, i.e. the swimming type of the fish, and therefore, it is assumed that lateral structures also evolve based on external loading conditions.

In standard topology optimization, the density at each material point is only constrained by the total volume of material. However, the activity of osteoblast and osteoclast is more a local phenomenon. Hence, the standard topology optimization problem is supplemented with a local density penalization to mimic this local phenomenon. To solve the optimization problem, a method based on a time dependent reaction-diffusion equation is employed [2]. The equation is driven by the sensitivity S , in which the Lagrangian multiplier λ is introduced. Solving this optimization problem gives an optimized structure with respect to the imposed boundary and loading conditions. The penalization term enables to control locally the feature size.

Using this equation, we developed a 3-D mathematical model to generate fish vertebra. Without local density penalization, thick beams appear similarly to the ridge structure. Penalizing locally the density, thinner beams are promoted and they tend to form a netlike structure. Numerical results show that the proposed model can produce both types of lateral structures, i.e. ridge structure and netlike structure, which are similar to the actual fish bone. In the future, it would be interesting to be able to produce various forms of fish vertebra by only adjusting a few parameters of the penalization law.

[1] Jang *et al.*, 2009

[2] Kawamoto *et al.*, 2013

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Model-based morphometrics for plant phenotyping

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Currently, high-resolution point cloud data can be acquired easily and cost-effectively. For example, a pipeline using Structure from Motion (SfM) and Multi-View Stereo (MVS), which is a promising technique to reconstruct a 3D surface as point cloud data from a series of 2D images taken from different angles, has been implemented in several libraries and software products. In this study, we developed a workflow for measuring and quantifying the canopy growth of soybean cultivars to compare growth speed based on point cloud data acquired from the SfM and MVS pipeline. First, we took multi-view 2D images of soybean plants growing in a field with a digital camera (EOS 60D, Canon, Tokyo). The images of plants in a single plot were taken from ca. 40 different directions. From these multi-view 2D images, point cloud data of soybean canopies were reconstructed by using the SfM and MVS pipeline. Second, we segmented the point cloud of plants and their leaves for each plot from the reconstructed data. Finally, we fitted several models to the point cloud data for estimating phenotypic values of plant organs constituting canopy architecture (e.g. leaf area, leaf shape, curvature). For example, we reconstructed 3D surfaces of leaves from the point cloud data with the penalized B-spline surface fitting by regarding a leaf as a 2D closed surface embedded in the Euclidean space \mathbb{R}^3 . When field conditions were not desirable (e.g. wind, change in light conditions)

for acquiring corresponding points among multi-view images, however, incomplete point cloud data were reconstructed.

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Using the classic Raup shell growth model as a morphometric tool to investigate genetic variation

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Two ecotypes of the marine snail species *Littorina saxatilis* have, as a result of strong natural selection, maintained different shell shapes in distinct, adjacent environments. Being able to quantify and compare the underlying growth structure for the two ecotypes should provide a better insight into the reasons behind the variability of shell shapes, and connect this to the genetics and selective pressures in their respective habitats.

Building on the ideas of Raup, we can construct models of snail shells using logarithmic curves containing a set of biologically descriptive growth parameters. This way of modelling illustrates the construction process of the shells, and the growth parameters are therefore expected to relate closely with the underlying genetics.

Previous biological shape research has mainly analysed the shells using variation of a set of landmarks after Procrustes alignment. This method can quantify the shape differences, but does not give an explicit explanation of how or why they occur. Because of the substantial amount of landmark coordinate data available for *L. saxatilis*, we have developed a geometric method for inferring the growth parameters from these points.

Applying this new analysis to snails collected across contact zones between ecotypes gives the result that growth parameters differ between them and that snails from the hybrid zone show intermediate values, which is consistent with the previous morphometric analysis. However, since the growth parameters are biologically meaningful they should be more informative from a developmental and genetic point of view, and we are going to investigate the performance of both shape characterizations in explaining the genetic variation.

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Joining forces: combining machine learning and mechanistic models to predict tumour cell density for glioblastoma patients

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Glioblastoma is the most aggressive primary brain cancer, with poor survival that can be largely attributed to intra-tumoural heterogeneity. While these tumours are primarily monitored via contrast-enhanced (CE) T1-weighted and T2-weighted magnetic resonance (MR) images, these standard clinical images are known to be non-specific in their correlation with tumour cell density. This lack of relationship makes it difficult to define the specific regions of interest to target for surgery and radiation. Previous efforts have shown some promise in better interpreting these images utilizing either machine learning (ML) or mechanistic modelling independently. But methods to harness the strengths of both approaches are sorely needed to make clinically actionable progress.

Here we present a novel, first-of-its-kind, hybrid model which brings together a graph-based semi-supervised machine learning approach with a mechanistic partial differential equation model of glioblastoma growth, known as the Proliferation-Invasion (PI) model, to generate predictive tumour cell density maps with high accuracy. Our ML approach bridges cell density as quantified from image-localized biopsies with texture analysis of multiparametric MR images. To incorporate the mechanistic model, the PI model is first used to generate an independent prediction of cell density which is then introduced into the ML algorithm through a Laplacian matrix, which ensures regions with similar predictions from the PI model will have similar predictions in the final model.

We have applied our proposed ML-PI model framework to 18 patients with a total of 82 image localized biopsies. Each patient's tumour was imaged with multi-parametric MR images, including T1-weighted, CE T1-weighted, T2-weighted, dynamic contrast-enhanced (DCE) imaging, diffusion weighted imaging (DWI), and diffusion tensor imaging (DTI). In this cohort, our hybrid model was able to achieve higher accuracy in cell density prediction than either of the independent models (ML or PI) alone, with a mean accuracy prediction error of 0.084 vs 0.227 for PI alone and 0.220 for ML alone. We hope that with more verification, this tool can be used to not only guide spatially localized therapies such as surgery and radiation, but also help broadly in the interpretation of images for glioblastoma patients.

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Heritable tumour cell division rate heterogeneity induces clonal dominance

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Tumours consist of a hierarchical population of cells that differ in their phenotype and genotype. This hierarchical organization of cells means that a few clones (i.e., cells and several generations of offspring) are abundant while most are rare, which is called clonal dominance. Such dominance also occurred in published *in vitro* iterated growth and passage experiments with tumour cells in which genetic barcodes were used for lineage tracing. A potential source for such heterogeneity is that dominant clones derive from cancer stem cells with an unlimited self-renewal capacity. Furthermore, ongoing evolution and selection within the growing population may also induce clonal dominance. To understand how clonal dominance developed in the iterated growth and passage experiments, we built three computational models that simulate these experiments. In the first two models we used the tau-leaping Gillespie algorithm to simulate random growth and passage and we either consider all cells to have an equal proliferation capacity (model 1) or we distinguish between cancer stem cells and differentiated cells (model 2). In the last model, we used a dynamic Monte Carlo method to simulate the development of a cell population where division rates are heritable and vary in between cells due to initial variation and mutation (model 3). Only simulations with the model where division rates varied between the cells (model 3) reproduced the clonal dominance that developed in *in vitro* iterated growth and passage experiments. In contrast, the experimental results

can neither be reproduced with a model that considers random growth and passage (model 1), nor with a model based on cancer stem cells (model 2). Altogether, our model suggests that *in vitro* clonal dominance develops due to selection of fast-dividing clones.

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The bone ecosystem

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Several types of cancer initiate or metastasize to the bone. These include the most prevalent and lethal cancers: lung, breast and prostate. Thus understanding the bone ecosystem is key if we want to predict what phenotypes will successfully metastasize to the bone and the subsequent evolutionary dynamics that will ensue as the invading tumour cells learn how to co-opt the bone resident cells. This bone ecosystem is very dynamic and responds and maintains homeostasis as micro and macro fractures appear. A variety of homeostatic processes emerge from the interactions of a myriad of cell types and signalling factors. Here I will present mathematical models, biologically motivated and tested, that explain bone repair and homeostasis and allow us to explore how tumours can grow in the bone as well as the impact of a variety of treatments not only on the tumour cells but also on the bone ecosystem.

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Direct parameterisation of an evolutionary game theory model from in vitro experiments

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Evolutionary game theory has been used to model cancer for more than a decade. Efforts to date have focused on understanding the effect of interactions between cancer cells of different types, and between aspects of the tumour microenvironment and cancer cells. To realise the full potential of these modelling efforts however, we submit that a method for direct parameterisation is required. In this talk, I will present our novel 'evolutionary game assay' designed specifically to parameterise a two strategy matrix evolutionary game from *in vitro* experiments comprised of co-culture of cells transfected with different colour fluorescent proteins. I will also show the results of the first game we measured, a game between EML4-ALK translocated non-small cell lung cancer cells before and after we evolved resistance to Alectinib (a targeted therapy). We find that these cells play either the Leader or Deadlock game, depending on different therapeutic and microenvironmental conditions. This change in game, as modulated by treatment, also suggests a novel therapeutic strategy which we have posited before is possible: treating the game instead of the player.

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A multiscale model to inform the design of nerve repair conduits

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Peripheral nerve damage afflicts 1 M people p.a. in Europe and the USA [1]. In the most severe cases, patients experience major loss of function. The gold-standard treatment for patients with severe cases is surgery using a graft based on a healthy section of nerve taken from the patient, however, only 50% of patients experience functional recovery [2].

After a nerve is severed, the distal stump produces chemotactic cues that can stimulate neurite regeneration. At the proximal stump, neurites start growing and their direction is informed by these cues. If the gap is short enough, the neurites are able to respond to their environmental cues and grow across the injury site to enter the distal stump. However, if the gap is larger than 5 mm, the regenerative process is unable to establish a supportive environment for neurite growth.

The limitations of the current gold-standard therapy to establish functional recovery have motivated the development of engineered replacement tissues and repair conduits to promote regeneration. Several designs have been proposed that vary not only in terms of material and therapeutic cell composition but also in their spatial distribution. Despite promising results in animal models, these conduits have not yet progressed to clinical use, in part because of the expanse of different variables that need to be tested using experimental models [3].

Here a multiscale mathematical model is proposed to streamline the design of these conduits. The model comprises of two components. The first is a continuous 3D model of the chemotactic field within the conduit. The release of chemotactic factors from the distal stump is captured using a flux boundary condition, as well as the permeability of the conduit wrap.

Within this geometry, at the proximal stump, a random walk model for individual neurites is initiated. Neurite growth is simulated as a random variable that is biased towards the direction of increasing cue; this cue could either be chemotactic (as described using the continuum model above), or durotactic (due to the underlying material distribution). Neurite branching is incorporated into the model, as this is a fundamental feature during regeneration, which determines how neurites sense the underlying gradient fields. Morphological features of branching are accounted for by implementing the model by Van Pelt *et al.*, whilst branches can also recede if they encounter a sub-optimal environment, modelled using a Markov chain process [4,5].

The discrete-continuum framework is parameterised against *in vitro* and *in vivo* data on neurite progression through engineered conduits, including neurite counts at the proximal and distal end as well as measurements of neurite lengths. The parameterised framework can be used to explore the optimal arrangement of materials and cells to promote efficient neuronal regeneration following injury.

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Homogenisation of a two-phase, elastic-poroelastic model of a fibre-reinforced hydrogels for tissue engineering of cartilage

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Tissue engineering aims to grow artificial tissues to replace those that have been damaged through age, trauma or disease. A recent approach to engineer artificial cartilage involves seeding cells within a scaffold consisting of an interconnected three dimensional printed lattice of polymer fibres combined with a cast or printed hydrogel, and subjecting the construct (cell-seeded scaffold) to an applied load in a bioreactor. A key question is understanding how the applied load is distributed throughout the construct to the mechanosensitive cells.

To address this question, we view the scaffold as a two-phase mixture, in which the fibres are modelled as a linear elastic material and the hydrogel as a poroelastic material. We exploit the disparate length scales (small inter-fibre spacing compared with construct dimensions) and use homogenisation theory to derive macroscale equations for the effective mechanical properties of the composite material. The resulting governing equations reflect the orthotropic nature of the composite. We then validate the model, by comparing results generated from finite element simulations of the macroscale, homogenised equations to experimental data describing the unconfined compression of the fibre-reinforced hydrogels.

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Multiphase modelling of early fibrous cap formation in atherosclerosis

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Atherosclerotic plaque growth is characterised by a process of chronic, non-resolving inflammation that leads to the accumulation of cellular debris and extracellular fat in the inner artery wall. In advanced plaques, smooth muscle cells (SMCs) are recruited from deeper in the artery wall to synthesise a fibrous tissue cap that sequesters the thrombogenic plaque content from the bloodstream. The fibrous cap therefore provides crucial protection from plaque rupture and the formation of blood clots that occlude vessels and cause heart attacks and strokes. Despite the important role played by the plaque fibrous cap in preventing the clinical consequences of atherosclerosis, the mechanisms that underlie cap formation remain poorly understood. In particular, it is unclear why certain plaques become strong and stable while others become fragile and dangerously vulnerable to rupture.

In this talk, we discuss the use of a multiphase approach with non-standard boundary conditions to investigate early fibrous cap formation in the intimal layer of the artery wall. We model the highly nonlinear process of SMC migration from the media in response to a diffusible chemical signal produced at the endothelium. Simulations indicate that the emergence of a stable fibrous cap requires a critical balance between the relative rates of cell supply from the media, chemotactic migration within the intima and cell loss by apoptosis (or phenotype change). Moreover, we identify a number

of disease-associated parameters that may be linked to variations in cap stability. This model represents the first detailed *in silico* study of fibrous cap formation in atherosclerosis, and establishes a framework that can be extended to investigate other aspects of plaque development.

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A multiphase model of glioblastoma multiform onset and growth

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Patients diagnosed with glioblastoma multiforme (GBM) are expected to survive only 14 months and die due to the pressure that the tumour builds in the brain as well as the formation of peritumoural edema (PTE). With the view to investigating the early stages of brain tumour development, and how it impacts the healthy brain environment, we develop a mechanistic model of GBM onset. The model is derived using principles of mass and momentum balances and explicitly includes pressure dynamics within the disease brain and the ability/inability of healthy tissue to repair itself in response to these cues. As a first step we assume an implicit tumour that exerts pressure at a healthy boundary causing the boundary to move into healthy tissue with a velocity v (thought of as the tumour growth rate). We investigate three velocity regimes: where v is an order of magnitude slower than the time-scale of healthy brain tissue renormalization (benign tumour); where v is an order of magnitude higher than the time-scale of healthy brain tissue renormalization (high grade tumour); a transition between these where v is the same magnitude as the time-scale of healthy brain tissue renormalization. Our model shows a correlation between the tumour velocity and the formation of PTE, which is an indicator of tumour malignancy. The resulting model includes time-varying diffusion on a moving domain, which presents unique numerical challenges. We propose a scheme to solve such equations, validating our method with a test problem as well as theoretical analysis using techniques from asymptotic methods in order to complete this research aim.

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Visualising mitochondrial networks in a beating heart cell

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Mitochondria are specialised organelles that produce adenosine triphosphate (ATP), a molecule used by cells as an energy source. Mitochondria form dynamic networks that constantly undergo fission and fusion in response to increased ATP demand. There is a lack of high-resolution data tracking the reorganisation mitochondrial networks in a beating heart cell. We use an agent-based model to simulate a mitochondrial network reorganising in beating heart cell. Our visualisation highlights how mitochondrial networks respond to a variety of stressors such as increased cellular respiration and localised hypoxia.

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Transport phenomena in field effect transistors

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Tailoring therapies to individuals for personalized care can be safer and yield superior outcomes with lower doses for conditions such as diabetes, Alzheimers disease, or even certain cancers. However, widespread use of personalized care is currently limited by our inability to routinely measure pathology and detect biomarkers. Moreover, existing strategies require specialized facilities, can be slow to perform and can be expensive. This has led to the development of a new portable detection tool known as a field effect transistor (FET). Very well-suited for biomarker measurements due their high charge sensitivity and direct signal transduction, FETs allow label-free measurements at physiological concentrations. Chemical reactants are injected at the top of a solution-well and diffuse through the well to bind with another chemical reactant immobilized to a narrow band on the well-floor. A resulting response curve allows for biomarker measurement and estimation of key parameters, such as binding affinities. A collection of mathematical models for FET experiments will be presented taking the form of a diffusion coupled to a nonlinear equation that describes the evolution of the reacting species concentration.

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A mathematical model of digestion in the colon

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The relationship between gut microbiota and health has been of keen interest for the past several years. The physical inaccessibility of the colon makes alternative research approaches a valuable addition to the clinical research done in this area. In this seminar, we discuss the compuGUT - a numerical simulation tool for studying anaerobic digestion and physiology in the colon. The underlying mathematical model is a system of partial differential equations with stiff, non-linear source terms. Our discussion will focus on the construction of the model, with additional discussion of the numerical implementation and applications of the software tool.

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Modelling transport in the placenta: scaling models to simulate organ level function

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The placenta is critical for our first nine months of life, as it provides nutrients from mother's blood and clears waste from the fetal circulation. The main structures that make up the placenta are villous trees, so called because they form a complex branching structure, like the branching of a tree, to provide a large surface area for exchange. Many pregnancy complications are associated with alterations in the structure of the villous trees and the blood vessels that reside within them. This potentially leads to poor matching of maternal and fetal blood flow rates at the site of exchange, and so impaired placental efficiency. Most computational models 'smooth out' the structure of the villous trees, or are limited to functional subunits of the placenta (placentomes) comprising just one of the 60-100 villous trees that comprise the placenta. Here I will present computational techniques to allow simulation of placental exchange at the whole organ scale, which include heterogeneity in villous structure. I will present evidence that the structure of the placenta is such that consideration of isolated placentomes is not always appropriate in simulation, and an analysis of how structural perturbations in the placenta (for example cord insertion at the periphery of the placenta) may impact on its exchange function.

Unravelling mechanisms underlying reproductive synchrony: from gene to ecosystems / 171

The evolution of a geographic cline in flowering time in bamboos

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Bamboos are clonal plants that undergo mass flowering followed by simultaneous death after a long-term period of rhizomatous vegetative growth. The time to flowering after germination depends on species and shows a geographic cline in which it is short in tropical region and becomes longer as we move to northward into temperate region. As another geographic tendency in bamboo, rhizome systems are different between tropical and temperate region. The species in tropical region have short and thick rhizomes, called pachymorph, resulting in clumped spatial arrangement of ramets. On the other hand, species in temperate region have long and slender rhizomes, called leptomorph. As a result, individuals are spatially intermingled each other. How these types of rhizome emerged in the evolutionary history and how the geographic correlation between flowering interval and rhizome system has been formed remains elusive. In this talk, using spatially explicit mathematical model, we explore the evolution of rhizome system in heterogeneous environment. We demonstrate that the longer rhizome is adaptive in relatively homogeneous environment, and short rhizome can evolve only when spatial autocorrelation of the quality of environment is high. We also demonstrate that flowering interval affects the evolution of rhizome length, in which long rhizomes are favoured when flowering interval is long. In addition to this, rhizome system, in turn, affects the evolution of flowering time.

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What drives reproductive synchrony of forest trees? Testing pollen coupling, veto and correlated environmental variation

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The highly variable and synchronized production of large seed crops by plant populations, called masting or mast seeding, has been reported across a broad group of plant species. While there

is consensus on the evolutionary drivers of masting, the proximate mechanisms are more controversial. Several hypotheses make predictions about the possible drivers of synchrony in masting species, including density-dependent pollination success (pollen coupling), environmental veto, or correlated environmental variation. The pollen coupling hypothesis predicts that weather and plant resources drive the flowering effort of trees, which directly translates into the size of seed crops through efficient pollination. In contrast, the veto hypothesis predicts that weather affects flower to seed transition, leading to occasional bumper crops. The recently formulated phenology synchrony hypothesis predicts that veto can arise because of weather effects on flowering synchrony, which, in turn, drives pollination efficiency.

I will first present the relationships between weather, airborne pollen, and seed production in common European trees, two oak species (*Quercus petraea* and *Q. robur*) and beech (*Fagus sylvatica*) with a 19-yr data set from three sites in Poland. Results show that warm summers preceding flowering correlated with high pollen abundance and warm springs resulted in short pollen seasons (i.e., high flowering synchrony) for all three species. Pollen abundance was the best predictor for seed crops in beech, as predicted under pollen coupling. In oaks, short pollen seasons, rather than pollen abundance, correlated with large seed crops, providing support for the veto effect and phenology synchrony hypotheses.

Next, I will show extended the resource budget model of masting with correlated reproductive failure (veto). We parametrized the model for five forest tree species (two oaks, two pines, and mountain-ash), and run the model for 500 yrs. In four out of five species, among-year variation in resource gain and correlated reproductive failure were necessary and sufficient to produce masting. In the fifth (*Quercus ilex*) veto and pollen coupling were also required. Mechanisms of masting clearly differ among species, but environmental variation may drive large-scale synchronization without any other synchronizing mechanisms in a significant pool of species.

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Mast seeding: puzzles and mathematical opportunities

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Mast seeding is the intermittent synchronous production of large seed crops by a population of perennial plants. This process is noteworthy in various ways. To the lay public, masting is noteworthy because it is very obvious when an occasional huge seed crop covers large areas.

In evolutionary terms it is noteworthy because delayed reproduction imposes inescapable costs on the plants, so it cannot occur unless there are compensating advantages (the search for which has occupied much of the relevant masting literature).

Ecologically it is noteworthy because of the need for a mechanism which can produce synchrony among plants, even though the plants cannot communicate. Most often this mechanism involves an external cue (usually weather), combined with some internal mechanisms such as resource sensitivity of flowering. Ecologically masting is also noteworthy because of the large downstream ecological consequences of pulsed resources.

Mathematically masting is noteworthy for four reasons. Firstly, masting is an emergent (population-level) phenomenon which reflects the sum of individual plant decisions. Constructing mechanistic models which have the right population-level properties is a challenge.

Secondly there is a competitive tension between model approaches which are driven largely by external cues (such as weather-cue models, with or without a resource veto), versus models largely driven by internal plant resource dynamics with some modest synchronizing cue (such as local pollen coupling or occasional flowering failure).

Thirdly some plant flowering time series are mathematically chaotic. Working out ways this complex population-level pattern can be created by simple within-plant mechanisms is interesting. One published example seems to have evolved because of selection on the plants for hard-to-predict time series.

Finally one of the proposed underlying mechanisms, the delta-T model, suggests plants are measuring a temperature difference across two summers and using that as the flowering cue. The mechanism by which plants could measure such a temperature difference is unknown. More interestingly, the delta-T model gives a better fit to some synthetic data which were created with a different underlying mechanism (resources plus last year's absolute temperature) than the real underlying mechanism does. Reasons for this implausibly good predictive ability of the delta-T model are currently unknown.

Unravelling mechanisms underlying reproductive synchrony: from gene to ecosystems / 152

Unravelling molecular basis of masting from transcriptome analysis and mathematical modelling

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The intermittent and synchronized production of a large amount of flowers and seeds is called masting or mast seeding. A family of resource budget models have been effective to evaluate proximate causes of masting. Applying recent advances in molecular and genetic studies about flowering time control to masting species is increasingly useful to unravel the underlying mechanism of masting. To uncover the molecular basis of masting, we performed global gene expression analyses in a typical masting species, *Fagus crenata* Blume. Using nonlinear time-series analyses, we examined causal relationships between gene expression, physiological status, and external environmental conditions. Our analyses unraveled the non-intuitive relationship between seasonal environment and expression profiles of genes involved in photoperiod and circadian clock pathways. The most striking result was the causal interaction between nitrogen transporter activity and expression of floral pathway integrator, *FLOWERING LOCUS T*. This result supports our previous finding that nitrogen is the key regulator of flowering in *F. crenata*. Our results highlight the importance of linking plant reproductive dynamics and nutrient cycling at ecosystem levels.

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Reproducing reproduction: understanding and modelling masting in European tree species

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Masting is the highly variable and synchronous production of seeds by plants. Masting can have cascading effects on plant population dynamics and forest properties such as tree growth, carbon stocks, regeneration, nutrient cycling, or future species composition. However, the spatio-temporal patterns and drivers of masting at the continental scale remain unknown. As a consequence, masting has often been missing from forest simulation models.

Here we detail the ongoing efforts to build a comprehensive dataset of seed production for the main European tree species. This dataset has been used, for example, to demonstrate that climate-masting relationships across the entire geographical range of European beech are (a) temporally and spatially consistent in the last century at the continental scale, and (b) are driven by low frequency modes of climate teleconnections (the Northern Atlantic Oscillation).

Our large research collaboration has also reviewed more than 200 published papers on mechanistic formulations of masting, to summarize how the main processes involved in masting and their related patterns (variability, synchrony, and frequency) can be incorporated into forest models with different degrees of complexity.

Future work will involve building empirical and mechanistic models to explore the tradeoffs between climate, resources, masting, and resource allocation, and using long-term, large-scale masting data to explore the effects of climate change on masting frequency, variability and synchrony at the population and continental scale.

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Fluid dynamics of nematocyst prey capture

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A nematocyst is a specialized organelle within cells of jellyfish and other Cnidarians that sting. Nematocysts are also present in some single celled protists. They contain a barbed, venomous thread that accelerates faster than almost anything else in the animal kingdom. Here we simulate the fluid-structure interaction of the barbed thread accelerating through water to puncture its prey using the immersed boundary method. For simplicity, our model describes the discharge of a single barb harpooning a single celled organism, as in the case of dinoflagellates. One aspect of this project that is particularly interesting is that the micron-sized barbed thread reaches Reynolds numbers above one, where inertial effects become important. At this scale, even small changes in speed and shape can have dramatic effects on the local flow field. This suggests that the large variety of sizes and shapes of nematocyst may have important fluid dynamic consequences. We find that reaching the inertial regime is critical for hitting prey over short distances since the large boundary layers surrounding the barb characteristic of viscous dominated flows effectively push the prey out of the way.

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Computational insights to high dimensional data from *Clostridium difficile* infection

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In recent years, new technology has allowed us to achieve measurements of hundreds of metabolites and the expression of thousands of genes. With this large scale, all-encompassing, 'omics' data comes a critical need to reduce these datasets to the most functional elements so that we can discover key components driving disease pathogenesis. Current techniques to analyze omics data are not geared towards supporting parsimonious mechanistic models of bacterial pathogenesis. Specifically, networks are common tools for analyzing these data, however, at times graphical networks can be overwhelming due to the complexity of the information. In this work, we use sparse graphical networks to understand correlations between multiple high dimensional data sets. We apply these method to metabolomics and transcriptomics data from a recent animal model for *Clostridium difficile* infection in which mice were antibiotic treated with cefoperazone and challenged with *C. difficile* 2 days following treatment. We find significant changes in the *C. difficile* transcriptome at later time points compared to earlier time points; while, most of the amino acid changes occur in the first 24 hours. We find taurine, proline, 3-(4-hydroxyphenyl)lactate, 5-aminovalerate, 5-oxoproline, thioproline are the main amino acids contributing to the changes across all time points. Utilizing the key components of the sparse graphical model we've developed and analyzed an ordinary differential equation model to better understand the specific mechanisms leading to *C. difficile* colonization.

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Modelling the argasid tick (*Ornithodoros moubata*) life cycle

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The first mathematical models for an argasid tick are developed to explore the dynamics and identify knowledge gaps of these poorly studied ticks. These models focus on *Ornithodoros moubata*, an important tick species throughout Africa and Europe. *Ornithodoros moubata* is a known vector for African swine fever (ASF), a catastrophically fatal disease for domesticated pigs in Africa and Europe. In the absence of any previous models for soft-bodied ticks, we propose two mathematical models of the life cycle of *O. moubata*. One is a continuous-time differential equation model that represents the tick life cycle with two stages, and the second is a discrete-time difference equation model that uses four tick stages. Both models use two host types: small hosts and large hosts, and both models find that either host type alone could support the tick population and that the final tick density is a function of host density. While both models predict similar tick equilibrium values, we observe significant differences in the time to equilibrium. These models provide the basis for developing future models that include disease states to explore infection dynamics and possible management of ASF.

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Stochastic models of epidemic super-spreading events

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The importance of host transmissibility in disease emergence has been demonstrated in historical and recent pandemics that involve infectious individuals, known as superspreaders, that are capable of transmitting the infection to a large number of susceptible individuals. To investigate the impact of superspreaders on epidemic dynamics, we formulate deterministic and stochastic models that incorporate differences in superspreaders versus non-superspreaders. In particular, continuous-time Markov chain models are used to investigate epidemic features associated with the presence of superspreaders in a population. We parameterize the models for two case studies, Middle East respiratory syndrome (MERS) and Ebola. Through mathematical analysis and numerical simulations, we find that the probability of outbreaks increases and time to outbreaks decreases as the prevalence of superspreaders increases in the population. In particular, as disease outbreaks occur more rapidly and more frequently when initiated by superspreaders, our results emphasize the need for expeditious public health interventions.

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Mechanical and experimental models of collective cell migration reveals the importance of intercellular interactions

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Scratch assays are routinely used to study the collective spreading of cell populations. In general, the rate at which a population of cells spreads is driven by the combined effects of cell migration and proliferation. To examine the effects of cell migration separately from the effects of cell proliferation, scratch assays are often performed after treating the cells with a drug that inhibits proliferation. Mitomycin-C is a drug that is commonly used to suppress cell proliferation in this context. However, in addition to suppressing cell proliferation, Mitomycin-C also causes cells to change size during the experiment, as each cell in the population approximately doubles in size as a result of treatment. Therefore, to describe a scratch assay that incorporates the effects of cell-to-cell crowding, cell-to-cell adhesion, and dynamic changes in cell size, we present a new stochastic model that incorporates these mechanisms. We then employ this stochastic model to quantify relative contributions of crowding effects and random motility into the collective cell migration in the scratch assay experiments containing malignant PC-3 prostate cancer cells.

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Mathematical and experimental models for wound closure in two dimensional “sticker” assays

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In order to explore the role of initial geometry in wound closure, we developed a new two-dimensional wound healing assay which we refer to as a sticker assay. Stickers are produced and attached to a tissue culture plate before cells are seeded into the centre of a dish. The stickers are then removed to leave a wound in the dish, which is an area with no cells. We performed a number of sticker assays using NIH 3T3 fibroblast cells and various initial wound shapes, including circles, squares, triangles and rectangles. By applying an edge detection method in ImageJ, we tracked the wound interface (and area) at discrete times up to 96h and found that different shaped wound closed at different rates. To explore these experimental results further, we applied two mathematical models, the first being a lattice-based random walk algorithm in two dimensions with nearest-neighbour exclusion, the second being a continuum-limit description based on the Fisher-Kolmogorov equation. By calibrating our models to the experimental data, we find that the parameter estimates for each initial wound shape are similar, suggesting that, while the closure rate is different for each initial wound shape, the underlying mechanisms that drive wound closure are the same. Finally, we revisit our continuum model by allowing for nonlinear degenerate diffusion of the type that occurs in the porous medium equation (characterised by an index n). We explore the hypothesis that circular wound closure is self-similar and circular wound boundaries are unstable for an increasing number of k -fold symmetric perturbations as the index n decreases. In particular, we highlight the consequences for wound closure with an initially rectangular wound, where both numerical and experimental results suggest that the wound becomes very long and thin in the limit that it closes.

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Mathematical modelling of the healing of venous leg ulcers

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A leg wound which does not heal because of problems with the veins in the leg is called a venous leg ulcer (VLU). Chronic VLUs are the most common chronic wounds in western countries and their treatment is both costly and time consuming. In this work, we present a mathematical model of the healing of a VLU which incorporates the key biological features of this wound type. We have modelled the role of oxygen, fibroblasts and extra-cellular matrix (ECM) within the wound site. The model consists of a system of nonlinear partial differential equations describing their interactions in space and time coupled with a moving wound outer boundary. The blood vessels that surround the wound supply the oxygen that is needed to support the processes of fibroblasts and ECM to repair the wound tissue. We consider a wound in a simplified one-dimensional geometry and the model equations are discretised in space using the finite difference method and then solved in MATLAB. Numerical results are presented for the oxygen, fibroblasts and ECM distribution within the wound space using parameter values sourced from literature, where possible. This model can be used as a predictive tool in a clinical setting to compare treatments of VLUs including compression bandages.

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Age structure as key to delayed logistic proliferation in scratch assays

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Scratch assays are standard *in vitro* experimental methods for studying cell migration. In these experiments, a scratch is made on a cell monolayer and imaging of the recolonisation of the scratched region is performed to quantify cell migration rates. Typically, scratch assays are modelled by continuum reaction diffusion equations depicting cell migration by diffusion and carrying capacity-limited proliferation by a logistic source term. In a recent work [1], the authors observed that on a short time, there is a disturbance phase where proliferation is not logistic, and this is followed by a growth phase where proliferation appears to be logistic.

In this talk, I will introduce an age-structured population model that aims to explain the two phases of proliferation in scratch assays. The cell population is modelled by a McKendrick-von Foerster partial differential equation. The conditions under which the model captures this two-phase behaviour are presented.

[1] Jin, W. *et al. Bull Math Biol* (2017)