



# SMB 2019 Annual Meeting

Montréal, Québec, Canada  
July 21-26, 2019

**From genome to biome**



**Society for  
Mathematical  
Biology**

Bienvenue à Montréal, the City with a French flavour at the interface of North American and European cultures. Our theme for this year's meeting is *From Genome to Biome* to illustrate the breadth of the biological scales at which mathematical methodologies are made to bare to further our understanding of all things biological, either within organisms or in the interaction of individuals, among themselves or with their environment. Scientific presentations at the meeting display the theory behind a number of medical interventions, and means to better grasp the powers at play in the environment.

This meeting would not have been possible without the technical support from many staff members of the Centre de recherches mathématiques, coordinated by Louis Pelletier, and the invaluable help of the Centre for Disease Modeling members recruited by Jane Heffernan. Although hosted in Montréal, the grinding groundwork required for such an event to take place was well distributed between the co-chairs of the Organising Committee. Sustainability considerations lead us to make this meeting BYOB (Bring Your Own Bag) and distribute the program and booklet of Abstracts in electronic form only.

Do enjoy the meeting, and your stay in Montréal !

Jane Heffernan, Jacques Bélair, Co-chairs, Organizing Committee

## **Organizing Committee**

Alexander Anderson, Julien Arino, Daniel Coombs, Frédéric Guichard, Thomas Hillen, Anmar Khadra, Stéphanie Portet, Ami Radunskaya, James Watmough, Huaiping Zhu

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# Sunday

Time	Plan
11:00 - 17:30	Workshop
14:30 - 16:30	Registration
17:00 - 19:30	Reception

**Registration** Registration is open from 9am to 4:30pm Mon, Tues, and 9am to 12noon on Weds. Please register at the Centre de Recherche Mathematique from 12noon on Weds to the end of the conference.

**Lunch** Lunch is served in Agora Morris et Rosalind-Goodman each day. This is located between Pavillon Jean-Coutu and Pavillon Marcelle-Coutu (No. 21 and 22 on the campus map).

**Health Breaks** Refreshments are served on the second and third floors of Pavillon Claire-McNicoll, the same building as all conference sessions (No. 15 on the campus map).

## Early Career Workshop (Detailed Schedule)

Pavillon Andre Aisenstadt (No. 20 on campus map), Room 1177

11:00 Introduction

11:30 How to get a tenure-track job (Robert Smith?)

13:30 Break

14:00 Working on your elevator pitch (Adriana Dawes)

14:45 Moving forward in academia: Empowering stories from SMB podcast interviews (Anet Anelone)

15:30 Introduction to the academic year mentoring pilot program (Elissa Schwartz)

16:00 Panel: Non-academic careers

# Monday

Time	Plan	Z-110	Z-200	Z-205	Z-209	Z-210	Z-215	Z-220	Z-245	Z-255	Z-260	Z-305
9:00 - 10:00	Plenary	Arthur Sherman (National Institutes of Health)						Type 2 diabetes: New equations, new thinking				
10:00 - 10:30	Break											
10:30 - 12:30	Minisymp.	Recent advances on immunobiology and modelling infection and subgroup dynamics of vector-borne diseases (1)	Using ecological theory to understand cancer	Recent perspectives on mathematical epidemiology	Mathematical modeling of normal and abnormal tissue growth and development	Spatial and evolutionary dynamics in mathematical ecology	Global Dynamics : Coexistence and Extinction in Mathematical Epidemiology (1)	Applications of mathematical techniques to neuroscience: from molecules to networks	Wave propagation in biological media (1)	Mathematical modeling of cellular transitions en route metastasis: epithelial-mesenchymal plasticity and associated cellular traits (1)		Mentoring Room
12:30 - 13:30	Lunch	Panel Discussion - Rules of life in the context of future math biology (Z-110)										
13:30 - 14:30	Plenary	Kim Cuddington (University of Waterloo)						Transients, autocorrelated variation, and invasive species impact				
14:30 - 15:30	Contributed Talks	CS1,0	CS 1,1	CS 1,2	CS 1,3	CS 1,4	CS 1,5	CS 1,6	CS 1,7	CS 1,8	CS 1,9	Mentoring Room
15:30 - 16:00	Break											
16:00 - 18:00	Minisymp.	Recent advances on algebraic tools for the modelling and biochemical dynamics of vector-borne diseases (1)	Algebraic analysis of reaction networks (1)	Modeling and analysis of the endocrine and neu-roendocrine systems	Data-driven methods for biological modeling (1)	Resource explicit population models	Modeling to conquer: understanding and controlling deleterious diseases using dynamical systems (1)	Population dynamics in heterogeneous landscapes: models, tool and data (1)	Modeling mosquito dynamics: the role of environmental diseases using dynamical systems (1)	Multiscale modeling of biofilms as complex ecological systems	Mathematical modeling of hematopoiesis under stress and disease (1)	Mathematical modeling in radiation oncology
18:00 - 21:00	Posters											

# Tuesday

Time	Plan	Z-110	Z-200	Z-205	Z-209	Z-210	Z-215	Z-220	Z-245	Z-255	Z-260	Z-305
9:00 - 10:00	Plenary	Lindi Wahl (Western University)										
10:00 - 10:30	Break											
10:30 - 12:30	Minisymp.	Modeling time since infection: theory and implications (1)	Immunobiology and Infection Subgroup (2)	Models of bacterial biofilms and biofilm control approaches	Contemporary mathematical approaches in developmental biology	Spatial and evolutionary dynamics in mathematical ecology	Math psychology and psychiatry	Mathematical modeling of cellular transitions en route metastasis: epithelial-mesenchymal plasticity and associated cellular traits (2)	Delay differential equation models in population biology	Mathematical modelling of hematopoiesis under stress and disease (2)	Spatial interactions in cell biology	Mentoring Room
12:30 - 13:30	Lunch	Women's Lunch(Z-110)										
13:30 - 14:30	Plenary	Mortiz Thon (Technical University of Munich) Morgan Craig (University of Montreal)				Toward a quantification of atherosclerosis Novel physiological mechanisms revealed through mechanistic modelling of granulopoiesis guides the optimization of chemotherapy regimens						
14:30 - 15:30	Contributed Talks	CS2,0	CS 2,1	CS 2,2	CS 2,3	CS 2,4	CS 2,5	CS 2,6	CS 2,7	CS 2,8	CS 2,9	Mentoring Room
15:30 - 16:00	Break											
16:00 - 18:00	Minisymp.	Modeling time since infection: theory and implications (2)	Immune system modeling in the context of cancer growth and treatment	Hepatitis B viral dynamics: mathematical and numerical methods	Mathematical Modelling of Cancer Therapy	Algebraic tools for the analysis of biochemical reaction networks (1)	Mathematical models for plants and biochemical signalling of cellular motility	The mechanics and development of mathematical drug transport	Applications of mathematical drug transport (1)	Modelling intracellular development of mathe- matical drug transport (1)	Modeling of the endocrine and neuroendocrine systems (2)	Data-driven methods for biological modeling (2)
	Business Meetings	MathEpi	MathImmuno		DevBio	EcologyEvol						
19:00 - 21:00	Posters											

# Wednesday

Time	Plan	Z-110	Z-200	Z-205	Z-209	Z-210	Z-215	Z-220	Z-245	Z-255	Z-260	Z-305	
9:00 - 10:00	Plenary	Helen Byrne (Oxford University)											
10:00 - 10:30	Break								AARMS Reception				
10:30 - 12:30	Minisymp.	Setup for AGM	Mathematical Modelling of Neuronal Networks (1)	Mathematical models for infectious disease at population level	Mathematical oncology from bench to bedside (1)	Stochastic models in micro and macro biological systems (1)	Population dynamics in marine ecology	Individual and agent-based models of within-host disease dynamics	Multiscale modeling of cytoskeleton-mediated cellular transport and aggregation (1)	Wave propagation in biological media (2)	Recent advances on modeling and dynamics of vector-borne diseases (3)		Mentoring Room
12:30 - 13:30	Lunch	AGM (Z-110)											
13:30 - 14:30	Plenary	Caroline Colijn (Simon Fraser University)											
14:30 - 15:30	Contributed Talks	CS 3,0	CS 3,1	CS 3,2	CS 3,3	CS 3,4	CS 3,5	CS 3,6	CS 3,7	CS 3,8	CS 3,9	MathWorks Workshop	
15:30 - 16:00	Break												
16:00 - 18:00	Minisymp.	Math psychology and psychiatry (2)	Modeling approaches in the development of cancer immunotherapies and their combinations	Agent-based models in mathematical biology	Population dynamics in heterogeneous landscapes: models, tools and data (2)	Stochastic models in micro and macro biological systems (2)	Modeling the impact of vector behavior, pathogen ecology, and environmental factors on the transmission of vector borne diseases	Modelling gene transcription (1)	Modelling gene transcription (1)	Analysis of doomed invasions in oncology, epidemiology and ecology (1)	Modeling in-host bacterial infections for prediction and prevention of disease	Recent advances on modeling and dynamics of vector-borne diseases (4)	Modeling to conquer: understanding and controlling deleterious diseases using dynamical systems (2)

Banquet

# Thursday

Time	Plan	Z-110	Z-200	Z-205	Z-209	Z-210	Z-215	Z-220	Z-245	Z-255	Z-260	Z-305
9:00 - 10:00	Plenary	Nick Monk (University of Sheffield) Mathematical Modelling in Biology: Integration and Differentiation										
10:00 - 10:30	Break											
10:30 - 12:30	Minisymp.	Mathematical Modelling of Neuronal Networks (2)	Stochastic models for biochemical reaction networks (1)	Building bridges for mathematical biology education (1)	Mathematical oncology from bench to bedside (2)	Global Dynamics : Coexistence (2)	Vector-borne diseases: improving and Extinction in Mathematical Models from Ecology and Epidemiology (2)	Mathematical modelling of bees and underlying mechanisms and implications for disease control	Modelling intracellular transport (2)	Modeling dynamics and control of African Swine Fever	Structured population models for disease transmission dynamics (1)	Disease and control
12:30 - 13:30	Lunch	Panel Discussion - Data Science Education for Biology (Z-110)										
13:30 - 14:30	Plenary	Naoki Masuda (University of Bristol) Network dynamics: Epidemic processes and energy landscape analysis										
14:30 - 15:30	Contributed Talks	CS 4,0	CS 4,1	CS 4,2	CS 4,3	CS 4,4	CS 4,5	CS 4,6	CS 4,7	CS 4,8	CS 4,9	Mentoring Room
15:30 - 16:00	Break											
16:00 - 18:00	Minisymp.	Mathematical Modelling of Neuronal Networks (3)	Advances in cancer treatment scheduling and optimization	Building bridges for mathematical biology education (2)	Mathematical modelling of protein misfolding disease	Stochastic biochemical reaction networks (2)	Validation of mathematical models in immunology and cancer	Modelling gene transcription and cancer	Multiscale modeling of cytoskeleton-mediated cellular transport and aggregation (2)	Modeling Cancer within the patient: a host-level focus	Optimization and optimal control in mathematical biology	Analysis of doomed invasions in oncology, epidemiology and ecology (2)
Business Meetings		MathNeuro	MathEd	MathOnco								

# Friday

Time	Plan	Z-110	Z-200	Z-205	Z-209	Z-210	Z-215	Z-220	Z-245	Z-255	Z-260	Z-240
9:00 - 10:00	Plenary	Jinzhi Lei (Tsinghua University)										
10:00 - 10:30	Break											
10:30 - 12:30	Minisymp.	<b>Mathematical Validation of Modelling of mathematical models in Neuronal Networks (4) Networks (4)</b>	Structured population models for immunology and cancer (2)	disease transmission dynamics (2)	Quantitative approaches to unravel immune function and immunity	Dynamics of immune system and cellular immunity	Mathematical functions at the cellular and molecular level	Cancer Therapy (2)				Mentoring Room
12:30 - 13:30	Closing Remarks											

# Carte du campus

- 1 Pavillon 520, chemin de la Côte-Sainte-Catherine  
 2 Pavillon 1420, boul. du Mont-Royal  
 3 Pavillon Marie-Victorin  
 4 Pavillon de la Faculté de musique  
 5 Centre d'éducation physique et des sports (CEPSUM)  
 6 Pavillon 2101, boul. Édouard-Montpetit  
 7 Pavillon J.-A.-DeSève (Centre étudiant)  
 8 Résidence C (étudiants et étudiantes)  
 9 Résidence A (étudiants)  
 10 Pavillon Thérèse-Casgrain (étudiantes)  
 11 École Polytechnique  
 12 Pavillons Pierre-Lassonde et Claudette McKay-Lassonde  
 13 Pavillon J.-Armand-Bombardier  
 14 Pavillon Roger-Gaudry  
 15 Pavillon Claire-McNicoll  
 16 Pavillon de la Direction des immeubles  
 17 Centre des technologies de fabrication de pointe appliquées à l'aérospatiale  
 18 Centrale thermique  
 19 Laboratoire René-J.-A.-Lévesque  
 20 Pavillon André-Aisenstadt  
 21 Pavillon Jean-Coutu  
 22 Pavillon Marcelle-Coutu  
 23 Pavillon Paul-G.-Desmarais  
 24 Garage Louis-Colin  
 25 Pavillon Samuel-Bronfman  
 26 Pavillon Maximilien-Caron  
 27 Pavillon Lionel-Groulx  
 28 Pavillon 3200, rue Jean-Brillant  
 29 HEC Montréal – Pavillon 5255, av. Decelles  
 30 Faculté de théologie, 3333, chemin Queen-Mary, 6<sup>e</sup> étage  
 31 Pavillon 3744, rue Jean-Brillant  
 32 3050 et 3060, boul. Édouard-Montpetit  
 33 3032 et 3034, boul. Édouard-Montpetit  
 34 2910, boul. Édouard-Montpetit  
 35 HEC Montréal – Pavillon principal  
 36 Pavillon de la Faculté de l'aménagement  
 37 2801 et 2815, boul. Édouard-Montpetit  
 38 Pavillon Liliane de Stewart  
 39 Pavillon Marguerite-d'Youville



## Mini-Symposia

## **Using ecological theory to understand cancer**

Adler, Frederick A, *University of Utah*

Griffiths, Jason I, *University of Utah*

### **Abstract**

The complexity of cancer has inspired the use of ecological thinking to understand the network of cell-cell and cell-environment interactions that make up the cancer ecosystem. Ecologists have long embraced the challenge of making sense of complex systems despite incomplete information about underlying mechanisms, and shown that carefully crafted theories provide precisely the tools needed to integrate the multiple streams of partial information into a useful whole. Speakers in the minisymposium will examine cancer from multiple theoretical perspectives, ranging from community ecology, behavioral ecology, restoration ecology, and evolutionary ecology.

**Monday, 10:30-12:30; Z-205**

Jason Griffiths

Irina Kareva

Robert Beckman

John Pepper

## **Vector-borne diseases: improving our understanding of underlying mechanisms and implications for disease control**

Agusto, Folashade, *University of Kansas*

Teboh Ewungkem, Miranda, *Lehigh University*

### **Abstract**

Infectious diseases are caused by different agents such as bacteria, viruses, fungi, protozoa, and helminths. Some of these disease agents are transmitted through the bites of infected arthropods such as mosquitoes, ticks, and sandflies. According to the World Health Organization, vector-borne diseases constitute more than 17 infectious diseases. In recent times, the number of vector-borne diseases emerging and re-emerging have been on the increase; for instance, 2013 saw the emergence of Chikungunya in the Americas. Similarly, the Americas witnessed the emergence of Zika in 2014. Aside from emerging vector-borne diseases, other diseases such as Leishmaniasis have been on the increase, with an estimated 200,000 to 400,000 new cases of Visceral Leishmaniasis occurring annually worldwide. On the other hand, malaria experienced a downturn in the number of cases from 2010 to 2015 as a result of active intervention. Hence it is imperative to review and improve our understanding of the underlying modeling mechanisms of these vector-borne diseases and their subsequent implications for disease control. Modeling, in particular mathematical, is, therefore, a powerful tool to devise a possible means of achieving permanent elimination of these diseases.

**Thursday, 10:30-12:30; Z-215**

Lauren Childs

Guido Camargo Espana

Jeffery Demers

Omar Saucedo

## **Applications of mathematical drug development**

Ahamadi, Malidi, *Merck Research Laboratory*

Mehta, Khamir, *Amgen*

Vargo, Ryan, *Merck*

### **Abstract**

Mechanistic mathematical models based on fundamental biochemical and physiological principles have been increasingly used to enable improved decision making at various stages in drug development process across pharmaceutical industry. This mini-symposium aims to present examples applications of such models, e.g. in making assessment of drug safety and efficacy, quantify first-in-human dosing strategy, dose optimization, optimal study design etc. The presenters will showcase and highlight the usage of quantitative mechanistic models that capture the essential elements of pharmacology to aid the optimization of treatment regimens. The diverse group of speakers bring together members of industry with that bring very different perspectives on how to implement and leverage mathematical models to answer specific questions in drug development. This mini-symposium will encourage the exchange of ideas and opportunities in using mathematical approaches in drug development and benefit both industry as well as academic participation.

**Tuesday, 16:00-18:00; Z-245**

Ryan Vargo

Chi-Chung Li

Khamir Mehta

Mindy Magee

## **Immune system modeling in the context of cancer growth and treatment**

Altrock, Philipp, *Moffitt Cancer Center*

Robertson-Tessi, Mark, *Moffitt Cancer Center*

### **Abstract**

The immune system is increasingly being recognized as a fundamental component of the tumor microenvironment that affects cancer progression at all stages from initiation to treatment. Given the immense complexity of the immune system, many details of tumor-immune interactions remain elusive. The non-linear, multi-dimensional nature of this interacting system provides ample opportunity for investigation with theoretical modeling. This minisymposium will offer four talks on important aspects of immune mechanisms that are relevant to oncology. In keeping with the theme of the conference, the speakers will present models that examine the immune system and tumor-immune interactions at different scales.

**Tuesday, 16:00-18:00; Z-200**

Ami Radunskaya

Luis Zapata Ortiz

Ardith El-Kareh

Morgan Craig

## **Mathematical oncology from bench to bedside**

Anderson, Alexander, *H. Lee Moffitt Cancer Center & Research Institute*

### **Abstract**

Mathematical modeling in oncology has a long history. Recent advances in mathematical oncology have focussed on a fully integrated, iterative workflow of experimental or clinical data motivating mathematical models, and model-generated hypothesis to inform subsequent validation experiments or clinical trials. This 2-part minisymposium showcases research from the SMB Mathematical Oncology Subgroup by members that are experts in either basic mathematical oncology (focus on experimental data and cancer biology questions) or translational mathematical oncology (focus on clinical data with oncology questions). Subjects vary from cancer development, progression and evolution to cancer treatment by radiotherapy, hormone therapy or chemotherapy.

**Wednesday, 10:30-12:30; Z-209**

Jacob Scott

Mohit Kumar Jolly

Russ Rockne

Gibin Powathil

**Thursday, 10:30-12:30; Z-209**

Eunjung Kim

Renee Brady

Thomas Yankeelov

Kristin Swanson

## Stochastic models for biochemical reaction networks

Anderson, David F, *UW-Madison*

Popovic, Lea, *Concordia*

### Abstract

Stochastically modeled biochemical reaction networks are used to model the time-evolution of biochemical processes when the counts of the constituent molecules are low. The standard model is a continuous-time Markov chain whose states represent the number of molecules present and whose transitions mark the occurrence of chemical transformations. In recent years stochastic models have been playing an increasing role in the mathematical biology literature. However, our understanding of their possible behaviors is still limited. For example, we still do not have robust/general results characterizing when a particular model is positive recurrent (stable), when it is explosive, when it will undergo an extinction event, etc. In this minisymposium, we attempt to bridge this gap by considering mathematical results that characterize the emergent behavior of these models. We will also consider computational methods for these stochastic models.

**Thursday, 10:30-12:30; Z-200**

David Anderson

Tung Nguyen

Andrea Agazzi

Jinsu Kim

**Thursday, 16:00-18:00; Z-210**

Badal Joshi

Chaojie Yuan

Andres Ortiz-Munoz

German Enciso

## Modeling and analysis of the endocrine and neuroendocrine systems

Bertram, Richard, *Florida State University*

Ha, Joon, *National Institutes of Health*

### Abstract

The endocrine system is composed of glands that contain hormone-secreting cells. The secretion of some hormones is under the direct control of the hypothalamus in the brain, forming the neuroendocrine system. Examples of endocrine glands are the pituitary, the adrenal, the pancreas, and the gonads. The hormones travel through the blood stream to target tissues throughout the body, including the brain, and regulate their function. They are responsible for mood, reproduction, sexual behavior, temperature and water regulation, growth, and glucose homeostasis, among many other things. The speakers in this minisymposium will discuss recent research utilizing mathematical models to understand the activity of cells in the endocrine or neuroendocrine system, and the effects of the released hormones on target tissue. The minisymposium is held in honor of Arthur Sherman, this year's Winfree Award recipient and a pioneer in the modeling and analysis of these systems.

**Monday, 16:00-18:00; Z-205**

Anmar Khadra

Eder Zavala

Joon Ha

Cecilia Diniz Behn

**Tuesday, 16:00-18:00; Z-260**

Benoit Huard

Brad Peercy

Patrick Fletcher

Richard Bertram

## **Mathematical Modelling of Neuronal Networks**

Best, Janet, *The Ohio State University, Mathematical Biosciences Institute*

Campbell, Sue Ann, *University of Waterloo*

Crodelle, Jennifer, *Courant Institute, New York University*

Ryu, Hwajeon, *University of Hartford*

Pyzza Pamela, *Ohio Wesleyan University*

### **Abstract**

Mathematical modeling is an important tool used to study neuronal dynamics and neural systems, leading both to better biological understanding of neuronal phenomena and to new mathematical questions. This session will feature recent contributions of mathematics to neuroscience, with an emphasis on the computation of neuronal networks in revealing underlying biological function.

#### **Wednesday, 10:30-12:30; Z-205**

Horacio Rotstein

Kanika Bansal

Daniel Park

Stefanos Folias

#### **Thursday, 16:00-18:00; Z-110**

Rodica Curtu

Yangyang Wang

Anca Radulescu

Janet Best

#### **Thursday, 10:30-12:30; Z-110**

Frances Skinner

Wilten Nicola

Shusen Pu

Youngmin Park

#### **Friday, 10:30-12:30; Z-110**

Cheng Ly

Christina Hamlet

Jennifer Crodelle

Pamela Pyzza

## **Modeling mosquito dynamics: the role of environmental variability**

Blackwood, Julie C, *Williams College*

Childs, Lauren M, *Virginia Tech*

### **Abstract**

Vector-borne diseases such as dengue, malaria, and Zika impact billions of people around the world. An essential component of their transmission cycle involves a life- cycle stage within the mosquito. In this mini-symposium, models of mosquitoes incorporating variability in stages will inform mosquito population dynamics. Such heterogeneity, altering population dynamics, can have important impact on transmission of vector-borne diseases.

#### **Monday, 16:00-18:00; Z-245**

Megan Greischar

Brandon Hollingsworth

Michael Robert

Kaitlyn Martinez

## **Applications of mathematical techniques to neuroscience: from molecules to networks**

Brake, Niklas, *McGill University*

Farjami, Saeed, *McGill University*

### **Abstract**

The brain is a highly complex system. To understand its behavior under (ab)normal conditions, researchers explore brain activity at many different levels: genetic, molecular, cellular, circuit, and network. Traditional biological approaches are not well adapted to complex, nonlinear interactions or large data sets, both of which are inherent to many areas of brain research. In this minisymposium, we intend to bring together scientists who take interdisciplinary approaches to answer questions related to brain dynamics. Topics covered in the minisymposium include all those that apply mathematical techniques to solve problems at various spatial and temporal scales of the brain in health and disease.

#### **Monday, 10:30-12:30; Z-245**

Niklas Brake

Saeed Farjami

Jonathan Rubin

Sue Ann Campbell

## **Spatial and evolutionary dynamics in mathematical ecology**

Cantrell, Robert S, *University of Miami*

Lam, King-Yeung, *The Ohio State University*

### **Abstract**

This workshop will focus on the spatial and evolutionary dynamics of organisms submitted to a changing environment. An interdisciplinary approach to the modeling and analysis of the problem will shed new light to this area. It is the goal of this mini-symposium to bring together biologists and mathematicians working on those problems, and to foster the development of new ideas and tools to understand the ecology of organisms in a changing world.

### **Monday, 10:30-12:30; Z-215**

Xiaoying Wang

Yuan Lou

Zhisheng Shuai

Guo Hongjun

### **Tuesday, 10:30-12:30; Z-210**

Joy-Ying Zhou

Robert S Cantrell

Chunhua Ou

King-Yeung Lam

## **Quantitative approaches to unravel immune function and immunity**

Cassidy, Tyler, *McGill University*

Craig, Morgan, *Université de Montréal*

### **Abstract**

Complex networks of cells and proteins regulate both immune cell production and function to protect the host against pathogenic intrusion. This minisymposium brings together researchers across disciplines to tackle quantitative aspects of immune function and immunity including host-pathogen and T lymphocyte trafficking kinetics, the role of iron during infection, and the instigation of immune response against cancer.

### **Friday, 10:30-12:30; Z-209**

Reinhard Laubenbacher

Tyler Cassidy

Amber Smith

Judith Mandl

## **Advances in cancer treatment scheduling and optimization**

Chamseddine, Ibrahim, *H. Lee Moffitt Cancer Center & Research Institute*

Rejniak, Katarzyna A., *H. Lee Moffitt Cancer Center & Research Institute*

### **Abstract**

Applications of anti-cancer therapies are faced with fundamental challenges, such as cell resistance, treatment toxicity, and physiological barriers to treatment delivery. The effectiveness of these therapies depends on cancer properties (tumor structure, microenvironmental heterogeneity), treatment properties (drug diffusivity, immune cell potency), as well as treatment scheduling and dosage. The rational selection of these multiple parameters to improve therapeutic efficacy and to reduce toxicological effects requires novel computational methods. In this minisymposium, our speakers will present recent advances in treatment planning methodologies and in developing robust treatment protocols taking into account tumor heterogeneity. We will also highlight the applications of optimization methods, widely used in engineering design, to develop effective cancer therapies. Our minisymposium will include applications in nano-, immuno-, adaptive and targeted therapies.

### **Thursday, 16:00-18:00; Z-200**

Jana Gevertz

Patrick Ellsworth

Ibrahim Chamseddine

Michael Kokkolaras

## Multiscale modeling of cytoskeleton-mediated cellular transport and aggregation

Ciocanel, Veronica, *Mathematical Biosciences Institute, Ohio State University*

Dawes, Adriana, *Department of Mathematics/Department of Molecular Genetics, Ohio State University*

### Abstract

Many cellular functions rely on active transport of components or nonrandom aggregation in order to promote gene expression, correctly position organelles, or activate signaling pathways. Cytoskeletal filaments such as actin and microtubules often play critical roles in these movement processes. In this minisymposium, speakers will present a number of different quantitative approaches to studying cytoskeleton-mediated transport and aggregation applied to biological systems ranging from mRNA localization in *Xenopus* embryos to receptor clustering in immune cells.

**Wednesday, 10:30-12:30; Z-245**

Adriana Dawes

Daniel Cortes

Garegin Papoian

Ying Zhang

**Thursday, 16:00-18:00; Z-245**

Jay Newby

Veronica Ciocanel

Diana White

Abhishek Choudhary

## Modeling to conquer: Understanding and controlling deleterious diseases using dynamical systems

Clifton, Sara M, *University of Illinois at Urbana-Champaign*

Rapti, Zoi, *University of Illinois at Urbana-Champaign*

### Abstract

The world's most harmful human diseases are complex dynamical systems. Mathematical modeling of disease dynamics, both within and between hosts, offers new insights into disease emergence, progression, transmission, and evolution. In this minisymposium, dynamical systems models will inform control strategies for a wide range of deadly human diseases, from malaria and Zika to cancer and polio.

**Monday, 16:00-18:00; Z-215**

Deborah Shutt

Kamaldeen Olatunde Okuneye

Sara Clifton

Hayriye Gulbudak

**Wednesday, 16:00-18:00; Z-305**

Adam Rhodes

Gregory Kimmel

Zoi Rapti

Celeste Vallejo

## Immunobiology and Infection Subgroup

Conway, Jessica M, *Pennsylvania State University*

Day, Judy, *University of Tennessee*

Reynolds, Angela, *Virginia Commonwealth University*

Smith, Amber M, *University of Tennessee Health Science Center*

### Abstract

The Immunobiology and Infection Subgroup was created to bring together researchers in the SMB community who are interested in the modeling and analysis of immune processes in human disease and of host-pathogen interactions. Our broad objective is to discuss various topics including - within-host infectious diseases - host immune responses - causes and effects of inflammation - disease progression and outcome - integration of experimental and clinical data into models - model-driven experimental design. In our 2019 minisymposium, we will focus on infection and host immune responses to both infectious and non-infectious insults. We will have 7 speakers with expertise in these areas. The talks will also showcase diverse modeling styles and integration with data.

**Monday, 10:30-12:30; Z-200**

Rustom Antia

Esteban Hernandez-Vargas

Rosemary Aogo

Carmen Lia Murall

**Tuesday, 10:30-12:30; Z-200**

Katharine Best

Chase Cockrell

Richard Allen

Jared Barber

## **Building bridges for mathematical biology education**

Diaz Eaton, Carrie, *Bates College*

Gaff, Holly, *Bates College*

Jungck, John, *University of Delaware*

### **Abstract**

This minisymposium will focus on bridge building for the future of mathematical biology education. We will explore approaches to teaching mathematical biology education using a variety of modalities to engage students, enhance learning, and enhance relevance to 21st century needs. We will also explore the interdisciplinary nature of our community, how new technology is changing that landscape, and what we can do as educators to meet these needs.

**Thursday, 10:30-12:30; Z-205**

John Jungck

Holly Gaff

Meredith Greer

Carrie Diaz Eaton

**Thursday, 16:00-18:00; Z-205**

Paul Macklin

Reggie McGee

Hwayeon Ryu

Eberhard Voit

## **Data science education for Biology (panel discussion)**

Diaz Eaton, Carrie, *Bates College*

**Lunch Panel, Thursday, 12:30-13:30; Z-205**

Lou Gross; Carrie Diaz Eaton; Holly Gaff

## **Validation of mathematical models in immunology and cancer**

Dobreva, Atanaska, *North Carolina State University*

Brady, Renee, *H. Lee Moffitt Cancer Center & Research Institute*

### **Abstract**

Mathematical models serve as invaluable tools in biomedical research, helping to uncover underlying disease mechanisms, analyze clinical data, and improve treatments. Achieving explanatory and predictive power requires that models are validated against data, observed biological behaviors, and known patient responses. This minisymposium will showcase validation techniques used in immunology and cancer, particularly to identify actionable biomarkers, make meaningful clinical predictions and evaluate therapeutic protocols. The session will cover methods including, but not limited to, simulation analysis, parameter estimation, sensitivity analysis, and uncertainty quantification.

**Thursday, 16:00-18:00; Z-215**

Maria D'Orsogna

Angela Reynolds

David Swigon

Atanaska Dobreva

**Friday, 10:30-12:30; Z-200**

Heiko Enderling

Susan Massey

Meghan Ferrall-Fairbanks

Angela M Jarrett

## **Modeling time since infection: theory and implications**

Earn, David, *McMaster University*

Dushoff, David, *McMaster University*

Feng, Zhilan, *Purdue University*

Glasser, John, *Centers for Disease Control and Prevention*

### **Abstract**

The classic SIR model that is attributed to Kermack and McKendrick was initially derived from their more general time-since-infection model by assuming that the infectious period is exponentially distributed. That is mathematically convenient, but biologically unrealistic, assumption characterizes much of the subsequent infectious disease modeling literature. We have invited a few of the researchers who in recent years have examined models with non-exponentially distributed stage durations. The goal of the symposium is to present the state-of-the-art in modelling this aspect of infectious disease transmission, and to consider its implications for data analysis and epidemic forecasting.

**Tuesday, 10:30-12:30; Z-110**

Maia Martcheva

Lorenzo Pellis

Zhilan Feng

John Glasser

**Tuesday, 16:00-18:00; Z-110**

Glenn Webb

Helen Wearing

David Champredon

David Earn; Jonathan Dushoff

## **Models of bacterial biofilms and biofilm control approaches**

Eberl, Hermann J., *University of Guelph*

### **Abstract**

Many bacterial infections are caused by bacterial biofilms, i.e. microbial depositions on biotic or abiotic surfaces. In engineered systems, such biofilms can enhance system failure, e.g. via microbially induced corrosion or biofouling. On the other hand many environmental engineering technologies are based on such biofilms. By 'biofilm control' we refer to measures that eliminate biofilms, prevent them or suppress their negative facets, or, in the case of beneficial biofilms, that enhance their performance. Biofilms are spatially and temporally heterogeneous systems, in which bacterial population and resource dynamics, cellular biochemistry, and physical processes are intertwined and interact. This minisymposium will focus on models of such multi-faceted interactions.

**Tuesday, 10:30-12:30; Z-205**

John Ward

Vincenzo Luongo

Harry Gaebler

Maryam Ghasemi

## **Mathematical modeling in radiation oncology**

Enderling, Heiko, *H. Lee Moffitt Cancer Center & Research Institute*

### **Abstract**

Since the early days of radiotherapy, mathematical modeling has played a pivotal role in analyzing radiosensitivity and calculating radiation treatment protocols. With increasing radiobiological knowledge and numerous biological agents that synergize with radiation, mathematical modeling is poised to continue to make significant contributions to the field of radiation oncology. In this minisymposium we bring together a group of leading international researchers from different research groups and hospitals that demonstrate the integration of experimental and clinical data to build mathematical models that help optimize cancer radiotherapy.

**Monday, 16:00-18:00; Z-305**

Sarah Bruningk

Jamie Dean

Juan Carlos Lopez Alfonso

Clemens Grassberger

## Modeling in-host bacterial infections for prediction and prevention of disease

Erwin, Samantha, *North Carolina State University*

### Abstract

Bacteria are mostly harmless single-celled organisms thriving in the human body. However, in some cases, these microbes can lead to disease states. This minisymposium features researchers from both mathematical and biological backgrounds who present recent modeling efforts to study infectious bacteria in-host including: *Clostridiois difficile*, *Mycobacterium tuberculosis*, and *Francisella tularensis*. Speakers will discuss a variety of mathematical techniques and tools used to study the different organisms such as agent-based models, graphical models, stochastic models, and ordinary differential equations. This session aims to bring together researchers of different backgrounds and expertise to encourage innovative approaches for modeling bacterial colonization and infection.

**Wednesday, 16:00-18:00; Z-255**

Denise Kirschner

Martin Lopez

Matthew Jenior

Samantha Erwin

### Individual- and agent-based models of within-host disease dynamics

Evans, Stephanie, *University of Michigan*

Renardy, Marissa, *University of Michigan*

Kirschner, Denise, *University of Michigan*

### Abstract

Individual/agent-based models have been used to study a wide range of diseases in a multi-scale manner. These models are important for determining mechanisms of disease initiation and progression, evaluating treatment protocols, and exploring the effects of heterogeneity within populations, tissues, and cell types. This minisymposium focusses on agent-based modeling of within-host disease development, and brings together different applications, modeling approaches, and methods for model analysis.

**Wednesday, 10:30-12:30; Z-220**

Gary An

Stephanie Evans

Jill Gallaher

Jesse Kreger

### Recent advances on modeling and dynamics of vector-borne diseases

Fan, Guihong, *Columbus State University*

Liu, Rongsong, *University of Wyoming*

Shan, Chunhua, *The University of Toledo*

Zhu, Huaiping, *York University*

### Abstract

Vector-borne diseases are a big threat to public health since some of them can kill an unprotected individual very quickly like malaria. The study of vector-borne diseases has become one of the most promising interdisciplinary areas in mathematical biology. This mini symposium will focus on recent advances on a variety of modeling and computational developments for studying vector-borne diseases. Topics cover malaria, West Nile virus, Lyme disease and etc. We highlight the importance of potential collaboration between mathematicians, entomologists, epidemiologist, and modelers in the prediction, prevention, and control of vector-borne diseases.

**Monday, 10:30-12:30; Z-110**

Jacques Belair

Jie Gao

Xi Huo

Ling Xue

**Wednesday, 10:30-12:30; Z-260**

Zhigui Lin

Luana Bassani

Ahmed Abelrazeq

Bruna Santos

**Monday, 16:00-18:00; Z-110**

Binxiang Dai

Shujing Gao

Rongsong Liu

Dane Patey

**Wednesday, 16:00-18:00; Z-260**

Daozhou Gao

Haitao Song

Chengjun Sun

Xianghong Zhang

## **Contemporary mathematical approaches in developmental biology**

Fletcher, Alex, *University of British Columbia*

Buttenschoen, Andreas, *University of Sheffield*

### **Abstract**

Recent technological advances have revolutionised the field of developmental biology: phenotypic analyses have been transformed from simple qualitative observations to quantitative characterisations, enabling the extraction of parameters with which to model complex processes and facilitating an unprecedented understanding of diverse aspects of development. As a result, this fast-moving field now impacts on key biomedical disciplines, from oncology to regenerative medicine. Alongside continual advancement of genetic and imaging techniques, developmental biology is increasingly benefiting from the use of mathematical modelling to help interpret and predict behaviour. Novel mathematical and computational tools are often required for model analysis. Key ongoing challenges in this area include understanding how single-cell behaviours determine tissue-level function, the roles of noise, the interplay between mechanical and chemical signalling, and the evolution of such mechanisms across species. The aim of this Developmental Biology Subgroup activity is to showcase the cutting edge of research in this area, with a focus on emerging talent. This will raise the profile of contemporary mathematical approaches to development within the SMB, encourage new members to join the Subgroup and work in the area, and provide a platform for new interactions between SMB members working in the area.

**Tuesday, 10:30-12:30; Z-209**

Adam MacLean

Lisanne Rens

Ruben Perez Carrasco

Renske Vroomans

## **Structured population models for disease transmission dynamics**

Gao, Daozhou, *Shanghai Normal University*

van den Driessche, Pauline, *University of Victoria*

Wu, Jianhong, *York University*

### **Abstract**

Structured population models provide an important framework to examine disease transmission through host-pathogen interaction when key structures such as demographic ages and physiological sizes, time since infection, and /or time since a particular intervention are important for the disease spread, prevention and control. Despite substantial advance in model formulation, analysis and applications, challenges remain. These challenges include: identification of structures; estimation of structure variables; data integration and data fitting to surveillance, field study and lab experiment data. This mini-symposium aims to present some samples of recent progress to address these challenges. The focus of eight invited speakers is expected to be (i). structured models for vector-borne disease transmission dynamics; (ii) system and structure identifiability; (iii). data fitting to estimate key epidemiological parameters and vector-host behaviors; (iv). impact of physiological structures on co-feeding transmission. This session is organized as part of the Canada-China bilateral collaboration, however, we have also secured substantial international participation with excellent diversity.

**Thursday, 10:30-12:30; Z-260**

Yijun Lou

Justin Munganga

Felicia Magpantay

Jorge Velasco Hernandez

**Friday, 10:30-12:30; Z-205**

Francesca Scarabel

Chadi Saad-Roy

Biao Tang

Jane Heffernan

## Multiscale modeling of biofilms as complex ecological systems

Ghasemi, Maryam, *University of Waterloo*

Mattei, Maria Rosaria, *University of Naples ‘Federico II’*

Polizzi, Bastien, *Institute Camille Jordan of the University of Lyon 1*

### Abstract

Biofilms are microbial communities on immersed surfaces, embedded in layers of a self-produced extracellular matrix, which mainly provide increased resistance against traditional methods of disinfection and eradication. Biofilms are ubiquitous and play beneficial or detrimental roles in many industrial and medical applications. For instance, they can lead to corrosion problems in freshwater pipes, and oil pipelines; they are recognized as the main cause of infections in host tissues or medical implants; they are involved in crop disease in plants and biofouling of industrial equipments. However, the adsorption and absorption properties and enhanced mechanical stability of biofilms make them advantageous to environmental engineering technologies, such as wastewater treatment, elimination of petroleum oil from contaminated systems or biofuel production. Understanding and mastering these systems is therefore a major industrial, economic and health issue. The processes and factors affecting biofilm growth are diverse and can be highly complex. They often involve direct and indirect interaction of several (up to hundreds) species including bacteria, micro-algae, archaea and fungi, complex biochemical reactions, and often depend on the physical conditions of the surrounding environment such as fluid dynamics and shear fields. Biofilm models are critical to improve our understanding of biofilm formation, structure and function. Mathematical models in this field range from stochastic individual based models to cellular automata models to deterministic continuum models. In many cases hybrid models are proposed to bridge various length and/or time scales, including PDE-ODE coupled systems of various types, mixed hyperbolic-elliptic free boundary value problems with non-local effects, etc. This raises the questions regarding well-posedness, stability, long term behavior and numerical treatment.

The aim of this minisymposium is to bring together researchers from the fields of Applied Mathematics more specifically Mathematical Biology with interest in diffusion-reaction equations, free boundary problems, mixture theory, multi-scale/multi-physics

phenomena, complex systems modeling and microbial population dynamics, providing a platform to discuss techniques and innovations related to modeling biofilm formation, growth, and morphology. Major emphasis will be placed on multi-scale models which describe biofilm development and its architecture under various environmental conditions. The minisymposium is intended for those studying biofilms in the context of complex ecological systems. The talks will be useful for researchers in the aforementioned fields as well as biofluids and biomechanics.

### Monday, 16:00-18:00; Z-255

David Chopp

Ana Carpio

Isaac Klapper

Sara Jabbari

## Mathematical modelling of hematopoiesis under stress and disease

Humphries, Tony, *McGill University*

Stiehl, Thomas, *Heidelberg University*

### Abstract

Hematopoietic stem cells (HSC) are responsible for life-long blood cell formation, and play a pivotal role in many diseases of the blood forming (hematopoietic) system. HSCs carrying mutations give rise to a wide range of diseases including pre-malignant and malignant diseases such as leukemias (blood cancers). Our intuitive understanding of the underlying dynamics is limited due to their complex and nonlinear nature. Mathematical models are an excellent tool to study complex phenomena and to provide insights into processes that cannot be measured directly. This minisymposium aims to bring together mathematical modellers and medical doctors contributing to a rigorous understanding of the hematopoietic system. The topics covered range from applied questions such as bone marrow transplantation, blood cancer evolution and cell-cell interactions in the stem cell niche to mathematical problems such as model reduction and multi-scale dynamics.

### Monday, 16:00-18:00; Z-260

Michael Mackey

Peter Ashcroft

Joseph Mahaffy

Anna Miller

### Tuesday, 10:30-12:30; Z-255

Thomas Stiehl

Kolja Eppert

Morten Andersen

Dominik Wodarz

## **Mathematical psychology and psychiatry**

Hurdal, Monica, *Florida State University*

Cochran, Amy, *University of Wisconsin-Madison*

Forger, Daniel, *University of Michigan*

### **Abstract**

Mathematics is important for addressing emerging challenges in psychiatry and abnormal psychology. One objective is to reorganize diagnostic criteria consisting of subjective symptoms, thoughts, and behavior into testable mathematical frameworks. For example, reinforcement learning provides a framework to understand human learning and decision-making and their neural correlates. Another mathematical direction lies in using dynamical systems to describe severe fluctuations in symptoms that mark chronic disorders such as depression, bipolar disorder, or schizophrenia. This minisymposium brings together a diverse group of researchers to highlight different mathematical approaches in psychology and psychiatry.

**Tuesday, 10:30-12:30; Z-215**

**Wednesday, 16:00-18:00; Z-110**

Daniel Forger

Monica Hurdal

Shelby Weaver

John Murray

Joel Nishimura

Amy Cochran

Zoran Tiganj

Jeff Dunworth

## **Delay differential equation models in population biology**

Hurford, Amy, *Memorial University*

Wang, Lin, *University of New Brunswick*

### **Abstract**

Delay differential equation (DDE) models consider dependencies on the past states of a population and many biological processes involve such dependencies. DDEs offer a realistic framework for modeling populations and novel dynamics may arise due to the delay-related assumptions. This minisymposium considers distributed, periodic, and dispersal delays and the population dynamics that arise from these model assumptions.

**Tuesday, 10:30-12:30; Z-245**

Gail Wolkowicz

Lin Wang

Kyeongah Nah

Fuxiang Li

## **Population dynamics in marine ecology**

Hurford, Amy, *Memorial University*

### **Abstract**

The dynamics of marine populations in distinct regions are linked by dispersal and movement, and the analysis of these spatially-explicit population models provides insight into the design of marine protected areas. This minisymposium will discuss next generation approaches, population models inspired by dynamic energy budget models, species interactions, behavior, and harvesting.

**Wednesday, 10:30-12:30; Z-200**

Frithjof Lutscher

Frederic Guichard

Peter Harrington

Joany Marino

## **Spatial interactions in cell biology**

Isaacson, Samuel A, *Boston University*

Zhang, Ying, *Boston University*

### **Abstract**

The dynamics of cellular processes can depend critically on interactions between particles undergoing spatial transport. Participants in this mini-symposium will investigate the effect of spatial transport and interactions on the dynamics of cellular processes. In particular, these include 1. The interplay between diffusion and clustering of transmembrane receptors on the surface of immune cells. 2. Interactions that facilitate the transport of proteins through nuclear pore complexes spanning the nuclear membrane. 3. Mechanisms by which mRNAs are trafficked both within and between cells within Drosophila oocytes. The mathematical models used to investigate these processes involve both deterministic PDEs and stochastic particle-based approaches, which will be studied by asymptotic analysis and novel numerical methods. In several cases, these modeling studies will be closely coupled to single-molecule imagine assays, which are common in calibrating model parameters and improving model accuracy.

**Tuesday, 10:30-12:30; Z-260**

Daniel Coombs

Alan Lindsay

Ruth Baker

Samuel Isaacson

## **Dynamics of immune system functions at the cellular and molecular level**

Jameldidine, Hassan, *McGill University*

### **Abstract**

The immune system plays a fundamental role in defending complex organism against pathogens, and in some cases can also trigger autoimmune diseases. The general theme of this mini-symposium involves the use of theoretical and computational approaches to understand the dynamics of various features of the immune response. Topics include viral infections, cytokine and metabolite profiles throughout the immune response, and population dynamics of immune cells. Speakers will present techniques used in their research to analyze these systems at the sub- and supra-cellular levels.

**Friday, 10:30-12:30; Z-210**

Alan Perelson

Hassan Jamaledine

Catherine Byrne

David Schneider

## **Modeling the impact of vector behavior, pathogen ecology, and environmental factors on the transmission of vector borne diseases**

Johnson, Leah R, *Virginia Tech*

Gaff, Holly D, *OldDominion University*

El Moustaid, Fadoua, *Virginia Tech*

### **Abstract**

Vector-borne diseases are indirectly transmitted infectious diseases that require the presence of a vector such as mosquitoes for Dengue, ticks for Lyme, and midges for Bluetongue disease. These vectors are highly sensitive to environmental conditions and very hard to control in order to monitor these diseases. This session will show a variety of mathematical and statistical models that have been used to understand the transmission process of vector-borne diseases as well as the role of environmental factors.

**Wednesday, 16:00-18:00; Z-215**

Fadoua El Moustaid

Cynthia Lord

Miranda Teboh Ewungkem

Marta Shocket

## Algebraic tools for the analysis of biochemical reaction networks

Johnston, Matthew D, *San Jose State University*

Meshkat, Nicolette, *Santa Clara University*

### Abstract

It is common to model the dynamical behavior of biochemical reaction networks such as signal transduction pathways and gene regulatory networks with a system of ordinary differential equations. The analysis of such systems has been crucial in understanding the biological mechanisms underlying such processes as apoptosis, circadian rhythms, and the cell cycle, and diseases like diabetes and cancer. Nevertheless, mathematical analysis of such models is challenging as a result of the high dimensionality of the systems, parameter uncertainty, significant nonlinearities, and time-scale separations between reactions. To address these challenges, tools from computational algebra and numerical algebraic geometry have been particularly fruitful and significant progress towards answering some of the more challenging questions in this area has resulted. In this session, we will give a forum to the latest advances on the analysis of such systems, with an emphasis on contributions from dynamical systems theory, algebraic geometry, and symbolic/numeric computation.

**Monday, 16:00-18:00; Z-200**

Elizabeth Gross

Nicolette Meshkat

Matthew Johnston

Adrian Tudorascu

**Tuesday, 16:00-18:00; Z-210**

Alan Rendall

Eduardo Sontag

Jiaxin Jin

Polly Yu

## Mathematical modeling of cellular transitions en route metastasis: epithelial-mesenchymal plasticity and associated cellular traits

Jolly, Mohit K, *Indian Institute of Science*

Levine, Herbert, *Rice University*

### Abstract

Metastasis – the cause of almost all cancer-related deaths – is a highly dynamic process where cells need to adapt to changing biochemical and biomechanical surroundings. No unique mutational signature has yet been associated with metastasis, emphasizing the importance of phenotypic plasticity – the ability of genetically identical cells to alter their phenotypes in response to many signals – in driving metastasis. Recent studies have identified the role of epithelial-mesenchymal plasticity in driving multiple facets of metastasis : collective cell migration, tumor-initiation, resistance against therapies including immunotherapy etc. A mapping of signaling networks driving this plasticity has motivated many mathematical models to elucidate the dynamics of such plasticity, to suggest experiments to quantify such plasticity, and to design treatment strategies to restrict this plasticity. This minisymposium focuses on inviting leaders in modeling cellular transitions during metastasis, and is proposed to last for two periods. The first period will involve speakers who have offered valuable insights into the intracellular and tissue-level dynamics of epithelial-mesenchymal plasticity, while the second period will gather experts who have investigated the emergence of EMT-associated cellular traits such as therapy/drug resistance and tumor-initiation potential, through mathematical modeling approaches.

**Monday, 10:30-12:30; Z-260**

Loukia Karacosta

Shubham Tripathi

Melissa Davis

Mingyang Lu

**Tuesday, 10:30-12:30; Z-220**

Kaitlyn Johnson

Mohammed Kohandel

David Wooten

Jason Somarelli

## **Optimization and optimal control in mathematical biology**

Kearsley, Anthony J., *National Institute of Standards and Technology (NIST)*

Melara, Luis, *Shippensburg University*

### **Abstract**

The minisymposium seeks to sponsor talks from graduate students, mid-level professionals and more senior researchers. The composition of the speakers is quite varied and with two graduate students and two professionals, one of whom is an academic and one who is working at a US national laboratory. Proposed Abstract: Solutions to most optimal control problems that arise in mathematical biology applications must be approximated by numerical methods. This minisymposium brings together several presentations that will introduce examples of these problems and will include newly developed mathematical models, novel mathematical analysis and specialized numerical approximation methods. Optimal control problems of ordinary and partial differential equations as well as of coupled systems will be considered.

### **Thursday, 16:00-18:00; Z-260**

Margaret Grogan

Anthony J Kearsley

Adarsh Kumbhari

Luis Melara

## **Disease and control**

Khan, Adnan, *Lahore University of Management Sciences*

Imran, Mudassar, *Gulf University of Science & Technology*

### **Abstract**

Compartment models have found wide applications in in-vivo and in-vitro modeling of dynamics of diseases and in their transmission. Therefore, modeling of disease control is typically based on these compartmental models using ordinary and partial differential equations and Markov process models. Optimal control techniques are an important mathematical tool to model transmission control and therapeutic control in non-infectious and in infectious diseases. This focus of this session is modeling the transmission dynamics and control strategies for infectious diseases. We aim to bring in people from a variety of geographical locations with modeling experience relevant to local problems.

### **Thursday, 10:30-12:30; Z-305**

Folashade Agusto

Mudassar Imran

Abba Gumel

Adnan Khan

## **Modelling gene transcription**

Kursawe, Jochen, *University of Manchester*

### **Abstract**

Abstract : Transcriptional gene regulation plays a key role in many biological contexts, including patterning during embryonic development and cellular timing. Existing models investigate the effect of spatial, stochastic and dynamic aspects of gene promoter regulation. The aim of this mini-symposium is to gather researchers from different fields of mathematics and biology who are interested in gene transcription in order to facilitate communication and work towards a greater understanding of transcriptional mechanisms. We focus on mathematical models that illuminate transcriptional regulation and on statistical approaches for interpreting experimental data on promoter interactions. Additional information : This mini-symposium proposal is relevant to multiple of the SMB subgroups, including Developmental Biology, Immunobiology and Infection, and Mathematical Oncology. The list of invited speakers achieves gender balance and geographical balance, with contributions from three different continents. If accepted, this mini- symposium will provide a platform specifically for outstanding early-career researchers. All listed speakers have agreed to present at this symposium.

### **Wednesday, 16:00-18:00; Z-220**

Huy Vo

Barbel Finkenstadt

Giorgos Minas

Rachel Waymack

### **Thursday, 16:00-18:00; Z-220**

Jacqueline Dresch

Jae Kyoung Kim

Cicely Macnamara

David Rand

## **Mathematical models for plants**

Ledder, Glenn, *University of Nebraska-Lincoln*

Russo, Sabrina, *University of Nebraska-Lincoln*

### **Abstract**

Plants play a critical role in Earth's environment, and it is important to understand their impact on climate change and the impact climate change has on them. This minisymposium looks at issues that arise in modeling of plant functioning, such as water flow in plants, stomatal control, and allocation of resources.

#### **Tuesday, 16:00-18:00; Z-215**

Danielle Way

Sabrina Russo

Nicholas Smith

Glenn Ledder

## **Modeling approaches in the development of cancer immuno-therapies and their combinations**

Lemaire, Vincent, *Genentech*

### **Abstract**

Cancer immuno-therapy is a cancer treatment that aims to improve or restore the patient's own immune functions in order to fight cancer development. The immune system and cancer are two of the most complex biological systems; understanding their interaction and controlling it is an even more challenging problem. The use of mechanistic modeling may help in the development of cancer immuno-therapies, in particular for questions involving the complex nature of these systems. These include intricate dose-response relationships, identifying signals of response, assessing synergy or sequencing effects in combination treatments, and assessing best target population. For this minisymposium, we gathered experts from academia and the pharmaceutical industry to discuss how modeling approaches may be used to aid in the development of cancer immuno-therapies, such as checkpoint inhibitors, T cell engaging molecules, oncolytic viral therapies, personalized cancer vaccines, cytokine-based therapies, and their combinations.

#### **Wednesday, 16:00-18:00; Z-200**

Vincent Lemaire

Mary Spilker

Roy Song

Andrzej Kierzek

## **Mathematical Modelling of Cancer Therapy**

Liao, Kang-Ling, *University of Manitoba*

### **Abstract**

The last few years, have seen many promising developments in cancer therapy including immunotherapy, radiotherapy, and chemotherapy. But there is still much work needs to be done to bring drugs from the bench through clinical trials. We need to find better ways to judge the success of the new therapies and to work out the optimal dose and treatment schedule. Right now, it is difficult to predict tumor response to a particular treatment by experiments or clinical trials. The long term benefits and remission of these new therapies are also not yet determined. Thus, the focus of this session will be on the combination of mathematical modeling and experiments to help overcome these problems.

#### **Tuesday, 16:00-18:00; Z-209**

SeokJoo Chae

Yangjin Kim

Kang-Ling Liao

Xiulan Lai

#### **Friday, 10:30-12:30; Z-215**

Wing Cheong Lo

Leili Shahriyari

Daewook Kim

Jaehyung Hong

# Population dynamics in heterogeneous landscapes: models, tool and data

Lutscher, Frithjof, *University of Ottawa*

Cobbold, Christina, *University of Glasglow*

## Abstract

Many populations live in heterogeneous environments, and individuals encounter habitats of significantly different quality. Fragmentation levels increase through human activities and other factors. Early models for population dynamics in such landscapes consisted of coupled systems of equations (one for each patch) and simple linear exchange terms between them. Recent modelling approaches include spatially explicit models with detailed individual-level movement descriptions. In all these models, the scale difference between regions of similar quality and the overall biological system play an important rôle. They allow us to study appropriate scaling limits (homogenization). This minisymposium will bring together modellers, analysts and empirical researchers to discuss the latest developments of such models, ranging from model formulation to analytical tools to data availability.

**Monday, 16:00-18:00; Z-220**

Christina Cobbald

Chris Cosner

Elizabeth Crone

Thomas Hillen

**Wednesday, 16:00-18:00; Z-209**

Nazanin Zaker

James Powell

Martha Garlick

JaneShaw MacDonald

## The mechanics and biochemical signalling of cellular motility

MacKay, Laurent, *McGill University*

Khadra, Anmar, *McGill University*

## Abstract

Cellular motility is critical for physiological processes such as embryonic development, localized immune responses, and wound healing. Furthermore, disruption of the machinery involved in motility is associated with pathological conditions such as metastatic cancer and autoimmune diseases. This minisymposium will focus on the dynamics which govern various aspects of cellular motility. The mechanical processes required to physically displace cells across space are regulated by biochemical pathways. Together, these lead to nonlinear dynamics resulting in complex spatiotemporal patterns of activity. These dynamics are analyzed using dynamic systems theory, producing theoretical predictions that allows us to further understand the motility machinery and how it may be harnessed for therapeutic purposes.

**Tuesday, 16:00-18:00; Z-220**

Laurent MacKay

Lennart Hilbert

Adam Hendricks

Leah Edelstein-Keshet

## Wave propagation in biological media

Mei, Ming, *McGill University*

Ou, Chunhua, *Memorial University of Newfoundland*

Wu, Yaping, *Capital Normal University*

## Abstract

Since the pioneer work of Fisher and KPP, Wave Propagation in Biological Media has been widely studied in various mathematical models establishing the movement or invasion of species in heterogenous media or the spread of infectious disease among species. Recently, there have been tremendous advancements in the theory of traveling wavefronts itself, with considerable applications to competition or predation models in the biological field. The purpose of this session is to invite mathematical researchers with biological backgrounds to work together and contribute to the study of biological waves. It will serve as a platform to report new breakthroughs, exchange research ideas and extend academic networks. New collaborations are also expected during and after the meeting. Speakers and talks are carefully selected to make the session attractive to a diverse audience. Especially, PhD students or post-doctoral fellows are encouraged to attend this session for getting research insight in their recent study.

**Monday, 10:30-12:30; Z-255**

Zhe Huang

Wan-Tong Li

Zhongwei Shen

Tianyuan Xu

**Wednesday, 10:30-12:30; Z-255**

Yuanwei Qi

Kun Zhao

Rui Huang

Chunhua Jin

## **Analysis of doomed invasions in oncology, epidemiology and ecology**

Milliken, Evan, *Arizona State University*

### **Abstract**

Stochastic models of population dynamics are used to study biological invasions in a wide variety of applications. Whether studying ecological invasion, success of a mutant species, metastasis or eradication of a tumor or outbreak or extinction of an infectious disease, important statistics of these models are the probability of and mean time until extinction. This mini-symposium proposes to bring together researchers studying the probability of and mean time to extinction using a wide variety of techniques including Little's Law, Galton Watson and multitype branching processes, local approximation in time and space, diffusion approximation, and Wentzel-Kramers-Brillouin approximation. Biological subject matter of the presentations will be varied.

**Wednesday, 16:00-18:00; Z-245**

Ohad Vilk

Malwina Luczak

Kaniz F Nipa

Julien Arino

**Thursday, 16:00-18:00; Z-305**

Fred Adler

Evan Milliken

Tom Chou

Peter Pang

### **Resource explicit population models**

Peace, Angela, *Texas Tech University*

Heggerud, Christopher M., *University of Alberta*

### **Abstract**

We present a collection of biological and mathematical findings in novel mathematical models where resource quantities are explicitly incorporated. The research presented will include an assortment of mathematical models based on biological stoichiometry where limiting resource quantity and quality are both present. Biological stoichiometry is the study of the balance of energy and multiple chemical elements in living organisms. Stoichiometric modeling, a relatively young branch of mathematical biology, has been greatly expanded in the past two decades, and population models inspired by biological stoichiometry have produced complex but strikingly realistic dynamical behaviors. Applications of resource explicit population models range from aquatic and terrestrial food webs, as well as within host systems such as cancer dynamics.

**Monday, 16:00-18:00; Z-210**

Christopher M Heggerud

Md Nazmul Hassan

Lale Asik

Angela Peace

### **Mathematical models for infectious disease at population level**

Ponce, Joan, *Purdue University*

### **Abstract**

Infectious diseases are caused by a wide variety of organisms such as bacteria, viruses, fungi and parasites. The dynamics of infectious diseases have been studied from several perspectives and levels (population and individual levels), which help determine transmission mechanisms of the diseases and effective forms of control. The main purposes of this session are i) bring together researchers working on modeling infectious diseases and share recent developments and modeling strategies ii) Foster connections between modelers of different scales of infectious disease processes: from individuals to the population level iii) Inspire questions and collaborations between early career and experienced researchers. Topics: Dr Christopher Kribs: "Invasion reproductive numbers for discrete and periodic systems" Pradyuta Padmanabhan: "Influence of Preventative Measures on the Spread of the Zika Virus" Joan Ponce: "Dynamics of a childhood disease model with isolation" Kyle Dahlin: "Mathematical Modeling of Avian Malaria in Hawaiian Honeycreepers"

**Wednesday, 10:30-12:30; Z-215**

Christopher Kribs

Joan Ponce

Kyle Dahlin

Pradyuta Padmanabhan

## **Mathematical modelling of bees**

Ratti, Vardayani, *Dartmouth College*

### **Abstract**

Pollinators, mostly bees, provide pollination for approximately 75% of the world's food crops. These pollinators however, are in significant decline globally, raising serious concerns about our food security and ecosystem stability. Mathematical modeling has greatly aided in understanding of these stressors and in suggesting remedial strategies using approaches from infectious disease modeling and theoretical ecology. The proposed minisymposium will bring together well-recognized speakers who are actively developing mathematical models on bees using differential equations techniques. The minisymposium will promote the communication and cross-fertilization of ideas amongst participants. This minisymposium follows similar and highly successful symposiums held at the SMB annual meetings in 2013, 2016, and 2017.

### **Thursday, 10:30-12:30; Z-220**

Hermann Eberl

Yun Kang

Nourridine Siewe

Ezio Venturino

## **Hepatitis B viral dynamics: mathematical and numerical methods**

Reinharz, Vladimir, *Institute for Basic Science*

Dahari, Harel, *Loyola University*

### **Abstract**

An estimated 300 million people are chronically infected with hepatitis B virus (HBV), the leading cause for hepatocellular carcinoma. This mini-symposium brings together modelers and mathematicians who are experts in the study of HBV dynamics and numerical methods to discuss current challenges in the field of viral dynamics with the emphasis on understanding viral-host interactions. This mini-symposium is targeted to both young and established mathematical modelers and clinical researchers interested in modeling HBV dynamics and immune responses.

### **Tuesday, 16:00-18:00; Z-205**

Stanca Ciupe

Jonathan Forde

Harel Dahari

Vladimir Reinharz

## **Stochastic models in micro and macro biological systems**

Rempala, Grzegorz, *The Ohio State University*

Kang, Hye-Won, *University of Maryland, Baltimore County*

### **Abstract**

Stochastic approaches to modeling phenomena in life sciences at various scales are becoming increasingly important as they allow to account for aggregate and disaggregate data, intrinsic and extrinsic biological noise, missing data and lack of experimental reproducibility. This minisymposium will cover several topics within broad area of stochastic modeling where recently some interesting advances have been made. The topics will include methods for aggregation/disaggregation of stochastic systems, parameter estimation, incorporation of network/contact structure, modeling of survival dynamics and stochastic compartmental models. They will be illustrated with examples from immunology and infectious diseases such as moderating immunoresponse or disease spread across scales, optimal contact tracing, mitigating transmission rates and network topology estimation.

### **Wednesday, 10:30-12:30; Z-210**

Jon Fintzi

Lea Popovic

Forrest Crawford

Wasiur Khudabukhsh

### **Wednesday, 16:00-18:00; Z-210**

Grzegorz Rempala

Daniel Linder

Hye-Won Kang

Boseung Choi

## Data-driven methods for biological modeling

Rutter, Erica, *North Carolina State University*

Nardini, John, *North Carolina State University*

Flores, Kevin, *North Carolina State University*

### Abstract

In the advent of big data and increased data availability in biology, mathematical modelers are faced with many opportunities and challenges, such as capturing heterogeneity, model selection and refinement, and utilizing multiscale models with data. This minisymposium will present advances in the development or novel application of statistical and machine learning methods towards modeling. These methods enable the use of mathematical models to assess hypotheses and propose biological mechanisms leading to the observed data. The first session applies data-driven methods to cancer, while the second session considers applications to a variety of biological phenomena such as wound healing, disease spread, and epidemiology.

**Monday, 16:00-18:00; Z-209**

Lee Curtin

Yang Kuang

Erica Rutter

Christina Vaghi

**Tuesday, 16:00-18:00; Z-305**

Harry Dudley

John Nardini

Suzanne Sindi

Marisa Eisenberg

## Global Dynamics : Coexistence and Extinction in Mathematical Models from Ecology and Epidemiology

Salceanu, Paul L, *University of Louisiana at Lafayette*

### Abstract

This minisymposium is intended to bring into discussion two fundamental outcomes of mathematical models from ecology and epidemiology : coexistence and extinction. A variety of aspects of analysis, including modeling techniques, numerical methods and the use of mathematical tools (such as stability analysis, bifurcation theory, persistence theory) are expected to be represented.

**Monday, 10:30-12:30; Z-220**

Linda Allen

Ruiwen Wu

Shigui Ruan

Xiunan Wang

**Thursday, 10:30-12:30; Z-210**

Jim Cushing

Amy Veprauskas

Alex Farrell

Zahid Mondal

## Rules of life in the context of future math biology (panel discussion)

Dawes, Adriana, *Ohio State University*

Eisenberg, Marisa, *University of Michigan*

Seshaiyer, Padmanabhan, *George Mason University*

## Lunch Panel, Monday, 12:30-13:30; Z-110

Adriana Dawes; Marissa Eisenberg; Padmanabhan Seshaiyer; Jim Powell; Junping Wang

## Mathematical modelling of protein misfolding disease

Sindi, Suzanne S, *University of California, Merced*

Pujo-Menjouet, Laurent, *University Claude Bernard Lyon 1*

### Abstract

Protein misfolding diseases, such as Alzheimer's and Parkinson's disease, result from the accumulation and aggregation of incorrectly folded proteins. These diseases can be genetic or spontaneous and in the special case of prion disease infectious. Because these diseases occur in different biological settings (e.g. humans, yeast) and time-scales (e.g. years, hours) a variety of mathematical models and experimental techniques have been employed. This minisymposium brings together biologists and mathematicians from a variety of fields with the goal of exploring the latest approaches towards studying protein misfolding diseases.

**Thursday, 16:00-18:00; Z-209**

Justin Torok

Paul Lemerre

Human Rezaei

Mikahl Banwarth-Kuhn

## **Recent perspectives on mathematical epidemiology**

Smith?, Robert, *Université d'Ottawa*

### **Abstract**

This minisymposium will bring together researchers to examine up-to-the-minute disease problems that showcase the usefulness and applicability of mathematical modelling to a world far beyond the mathematical community. The audience is the mathematical biologist with an interest in infectious disease. This includes students and researchers, mathematicians interested in seeing applications and biologists who wish to see how mathematics can be used to solve real problems. The minisymposium is interdisciplinary in nature and includes those trained as mathematicians, epidemiologists and immunologists.

**Monday, 10:30-12:30; Z-209**

Robert Smith?

Aili Wang

Cameron Browne

Katie Vogt Geisse

## **Agent-based models in mathematical biology**

Strickland, Christopher, *University of Tennessee*

### **Abstract**

Agent-based models are models in which individuals are described as autonomous entities which can then interact with each other and/or their environment. They are particularly well suited to exploring ways in which individual-level behavior can result in emergent population-level patterns – patterns which in turn often yield a nice mathematical description. Agent-based models are also useful for developing effective control strategies in stochastic systems with complex individual-level interactions. In this minisymposium, we will explore several ways in which agent-based models are being used in mathematical biology, by examining the behavioral response of swimmers in porous-layer fluid flow, the mechanics of pattern formation in locust swarms, control strategies for infection in healthcare facilities, and optimal spatiotemporal harvest strategies in agricultural settings.

**Wednesday, 16:00-18:00; Z-205**

Christopher Strickland

Jasmine Kreig

Brittany Stephenson

Andrew Bernoff

## **Modeling Cancer within the patient: a host-level focus**

Wilkie, Kathleen, *Ryerson University*

### **Abstract**

Cancer does not grow in isolation. It grows within a body, constantly receiving and sending signals that alter the future state. This mini symposium will look at ways in which the body alters tumour fate (such as immune responses), or at ways in which tumours alter the body, (such as cancer cachexia).

**Thursday, 16:00-18:00; Z-255**

Suzan F Sardroodi

Chiara Nicolo

Adrienne Jenner

Kathleen Wilkie

## **Mathematical modeling of normal and abnormal tissue growth and development**

Wu, Min, *Worcester Polytechnic Institute*

### **Abstract**

The minisymposium is intended to describe the contributions of mathematical modeling and computation to topics at the interface between developmental biology and oncology. Topics of 1) brain tumor development, 2) growth regulation in intestinal crypts, 3) pancreatic cancer invasion in extracellular matrix and 4) cell intercalations during Drosophila germband extension will be presented to gain a broader understanding of the similarity and difference between normal growth and abnormal growth.

**Monday, 10:30-12:30; Z-210**

Vivek Shenoy

Clinton Durney

Axel Almet

Meghan Hall

## **Modeling, dynamics and control of African Swine Fever**

Zhang, Xianghong, *York University*

Li, Juan, *China Animal Health and Epidemiology Center*

### **Abstract**

Brief abstract: African swine fever (ASF), caused by African swine fever virus (ASFV), is a highly contagious virus causes high fever, hemorrhages, ataxia, and severe depression in domestic pigs and wild boar, a notifiable threat to the World Organization for Animal Health. ASFV has swept over many countries including Caucasus, European countries and the Baltic countries. In August 2018, the first outbreak of ASF was reported in Liaoning province, China, since then it has rapidly spread to over 25 provinces in China, causing 102 outbreaks till the end of January 2019. The spread of ASF in China has posed serious threat on both local and the world pig industry. Both Canada and USA have serious concerns of the spreading of the virus due to vast and rapid human travel and globalized trade. This mini-symposium, the few interdisciplinary speakers will focus on recently modeling, dynamical and computational study of the transmission and control of ASFV.

**Thursday, 10:30-12:30; Z-255**

Xinmiao Rong

Liping Wang

Pei Yuan

Juan Li

## **Modelling intracellular transport**

Zhelezov, Gleb, *University of Edinburgh*

Chumakova, Lyubov, *University of Edinburgh*

### **Abstract**

Cellular components are delivered to their biologically relevant locations by molecular motors moving along the cytoskeleton. Correct outcomes of this intracellular transport is crucial to the proper cellular, and therefore, organismal, function. Among the processes strongly reliant on intracellular transport are cell-cell adhesion, cell division, and cell motility. Our proposed minisymposium is aimed at modelers of intracellular transport, who are in active conversation with biologists. Although intracellular transport is an active research area in experimental biology [1], and has also been the focus of some modelling work in the mathematical biology community [2], several recent advances in the field are the result of collaborative investigations between mathematicians and cell biologists. Today, mathematical modelling is not only used to explain experimental results, but also to guide experiments. The goal of this minisymposium is to highlight such projects. This session will not only serve as a platform for disseminating novel research results, but will also present an opportunity for the mathematical community to discuss how to effectively communicate research with cell biologists, and work around experimental constraints. The invited speakers are a diverse, gender-balanced group, at different career stages. [1] J. L. Ross, M. Y. Ali, D. M. Warshaw, Cargo transport: molecular motors navigate a complex cytoskeleton. *Current Opinion in Cell Biology*. 20 (2008), pp. 41–47. [2] C. Appert-Rolland, M. Ebbinghaus, L. Santen, Intracellular transport driven by cytoskeletal motors: General mechanisms and defects. *Physics Reports*. 593 (2015), pp. 1–59.

**Tuesday, 16:00-18:00; Z-255**

Gleb Zhelezov

Stephanie Portet

John Fricks

Calina Copos

**Thursday, 10:30-12:30; Z-245**

Lyubov Chumakova

Aleksandra Plochocka

Eric Cytrynbaum

Thomas Fai

## Contributed Talks

Monday, CS 1

Buttenschoen, Andreas	Spatio-temporal heterogeneities in a mechano-chemical model of collective cell migration
Owen, Jennifer	Understanding zebrafish pigment pattern formation using mathematical modelling
Zmurchok, Cole	Modeling cell shape diversity arising from complex Rho GTPase dynamics

Monday, CS 2

Faria, Matthew	Determination of a kinetic model of nanoparticle-cell interaction
Ruegg-Ereymond, Pauline	Pre-menstrual inflammatory processes in the uterine endometrium
Van Steijn, Leonie	Modeling zebrafish metabolism

Monday, CS 3

Dobrovolny, Hana	An agent-based model of viral transmission
Hult, Caitlin	Understanding the role of neutrophils in M. tuberculosis infection: Modeling approaches and visualization techniques
Islam, MD Rafiul	Identifying the dominant transmission pathway in a multi-stage infection model of the emerging fungal pathogen Batrachochytrium salamandrivorans on the Eastern Newt

Monday, CS 4

Hurford, Amy	Eliminating stage-structured pests with temperature-dependent life histories
Jung, Eunok	Dynamical Models of the 2009 A/H1N1 Influenza and Effective Intervention Strategies in the Republic of Korea
Omori, Ryosuke	Difference in seasonal variations between transmission rate and re-activation rate explains the epidemic curves of Varicella and Zoster

Monday, CS 5

Ballesta, Annabelle	P-glycoprotein (Abcb1) expression and activity are sex-, feeding-, and circadian time-dependent, implications for mechanistic pharmacokinetics modeling
Fry, Brendan	Modeling bloodflow and oxygenation in a retinal microvascular network
Voorsluijs, Valerie	Impact of mitochondrial exchanges on calcium wave propagation in astrocytes

Monday, CS 6

Abler, Daniel	Capturing variability of tumor-induced mass-effect in glioma growth models
Basanta, David	Evolutionary tempo and the tumor microenvironment
Jerry, Chakib	Controlled Switched System for Cancer Model

Monday, CS 7

Karev, Georgiy	Struggle for Existence: models for Darwinian and non-Darwinian selection
Li, Guanlin	Why be Temperate: On the Fitness Benefits of Lysis vs. Lysogeny
Rouzine, Igor	Evolutionary footprint of epistasis

Monday, CS 8

Campos, Paulo	Functional specialization under multiple tradeoffs mediated by resources
Hurtado, Paul	A General 'Linear Chain Trick' for building ODE models with flexible dwell times
Kelly, Michael	Marine Reserves and Optimal Dynamic Harvesting When Fishing Damages Habitat

Monday, CS 9

Tuesday, CS 1

Dallon, John	A Stochastic Model of Filament Transport by Motor Proteins
Kursawe, Jochen	Stochastic amplification of gene oscillations during embryonic neurogenesis
Roussel, Marc	Developing a left and a right side: bistability in the Lefty-Nodal network

Tuesday, CS 2

Anelone, Anet	Elite control of HIV exhibits some robustness properties
Cao, Youfang	Mechanistic Immuno-Viral Dynamics Modeling Platform for HIV Cure Drug Development
Stroberg, Wylie	Information Processing by Endoplasmic Reticulum Stress Sensors

Tuesday, CS 3

Adekunle, Adeshina	A pandemic tool for emerging disease monitoring: Ebola as a case study
Pedro, Cardenas	Qualitative behavior of AIDS in a homosexual population
Schmidt, Deena	Contagion dynamics on adaptive networks: Norovirus as a case study

Tuesday, CS 4

Arceo, Carlene	Stochastic SEIR Dynamics on an Edge-based Network Model
Jiao, Jing	The influences of host evolution on host-pathogen interactions across space
Milwid, Rachael	Assessing the impact of empirical contact patterns on disease dynamics within an equine population

Tuesday, CS 5

Bulai, Iulia Martina

Geometrical analysis of mixed-mode bursting oscillations in a multiple-timescale model of bursting electrical activity

Fokoue, Diane

Numerical Methods for the Microscopic Cardiac Electrophysiology Model

Ly, Cheng

Spike statistics during olfactory stimulation via orthonasal and retronasal inhalation

Tuesday, CS 6

Maestrini, Davide

On the concept of temperature in the process of aging and AML development

Sahoo, Prativa

Mathematical modeling to quantitatively evaluate the dynamics of CAR T-cell therapy in glioblastoma

West, Jeffrey

Tissue structure accelerates evolution: premalignant sweeps precede neutral expansion

Tuesday, CS 7

Brunner, James

Modeling microbial community dynamics using genome scale metabolic models.

Collera, Juancho

HOPF BIFURCATION IN A THREE-SPECIES INTRAGUILD PREDATION MODEL WITH STAGE STRUCTURE

Humphries, Tony

Equivalences Between Age Structured Models and Distributed Delay Differential Equations

Tuesday, CS 8

Arumugan, Ramesh

Tracking unstable states: A complicated dance in a changing world

Laverty, Sean

Modeling woundwood rib formation and fire scar closure in fire-scarred oaks

Liu, Pengyu

A polynomial metric on rooted binary tree shapes

Tuesday, CS 9

Deka, Aniruddha

Individual vaccination choice and optimal budget allocation for vaccination campaign

PuelmaTouzel, Maximilian

Inferring population dynamics from high-throughput sequencing

Kose, Emek

Modeling the Stem Cell Hypothesis for Cancer

Wednesday, CS 1

George, Uduak

Stretching the Embryonic Lung Tissue May Affect the Length of its Epithelial Tubes

Sadria, Mehrshad

Network Analysis of Eye-Gaze Pattern in Autism

Stefaniak, Elisa

On the probability distribution of resource allocation strategies in plants

Wednesday, CS 2

Bridge, Lloyd

LINEAR TRANSIT COMPARTMENT PHARMACOKINETIC MODELS AND EQUI-DOSING REGIMEN REGIONS

Jegatheesan, Thulasi

Model-Based Analysis of Recovery of Gut Microbiota after Antibiotic Disturbance

Strube, Laura

Activation of the integrated stress response: Does it tune or tame?

Wednesday, CS 3

Fu, Feng

Evolutionary Game Theory with Applications to Behavioral Epidemiology

Phillips, Tricia

Modeling the Heroin Epidemic

Renardy, Marissa

Evaluating vaccination strategies for tuberculosis in endemic and non-endemic settings

Wednesday, CS 4

Mema, Ensela

Modeling the Influence of Social Interactions on Physical Fitness

Volkening, Alexandria

Forecasting elections using compartmental models of infection

Ye, Ping

Prenatal alcohol exposure in American Indian and Caucasian mothers in the US Northern Plains

Wednesday, CS 5

Latulippe, Joe

A mathematical model of the effects of Amyloid beta on IP3 signaling mechanisms.

MacLaurin, James

Phase Reduction and Synchronization Through Environmental Noise in Stochastic Biochemical Oscillations

Stolerman, Lucas

Stability analysis of a bulk-surface model for membrane-protein clustering

Wednesday, CS 6

Przedborski, Michelle

A systems biology approach to study adaptive drug resistance in acute myeloid leukemia

Robertson-Tessi, Mark

Evolution of T-cell receptors in the context of cancer and self-antigens

Sordo Vieira, Luis

An intracellular model linking iron metabolism to the cell cycle

Wednesday, CS 7

Basiri, Maryam

Pushing Boundaries: The existence of solutions for a free boundary problem modelling the spread of ecosystem engineers

Marleau, Justin

When activators become inhibitors: emergent spatial patterns in meta-ecosystems

Sheppard, Lawrence

Examining the plankton paradox with timescale-specific predictors of abundance changes

Wednesday, CS 8

Calcagno, Vincent

Life is not a long quiet river: modelling population genetic divergence when migration is fluctuating

Morris, Tricia

Modelling the evolution of flowering onset in perennial plants

Ryan, Shawn

Mathematics Provides Insight into Self-Organization in Biology

Wednesday, CS 9

Thursday, CS 1

Fuhrman, Kseniya

Progression of Numerical Techniques for Model Construction and Analysis

Sun, Anthony

On the mathematical form of an incentive in a socio-ecological model

Zobitz, John

Development of computational tools in R for an undergraduate mathematical biology and modeling course

Thursday, CS 2

Berezovsky, Faina

Modeling of "replicator - genetic parasites" dynamics and coexistence

Bitsouni, Vasiliki

Modelling calcium signalling in cancer growth

Wu, Min

Stress generation, relaxation and size control in restricted tumor growth

Thursday, CS 3

Bannish, Brittany

Effects of clot contraction and fiber distribution on blood clot degradation

Moran , E Joe

Understanding rabies persistence in low density fox populations

Rozins, Carly

Can phage therapy replace antibiotics?

Thursday, CS 4

Myerscough, Mary

A Structured Population Model for Lipid Accumulation in Macrophages

Pinky, Lubna

Quantifying Kinetic Differences in Two Recombinant Parainfluenza Viruses

Stockdale, Jessica

Modelling and genomics to identify dangerous Streptococcus pneumoniae strains

Thursday, CS 5

Means, Shawn

Weaving a Tangled Web: Neurons and Networks

Parsons, Sean

Coupled oscillators in the gut

Roberts, Paul

Investigating the functional connectivity of the zebrafish retina

Thursday, CS 6

Abbas, Fazal

A New Approach to Substrate Flux Approximation for Monod Boundary Value Problem Arises in the Study of Biofilms

Gjini, Erida

How mathematical modeling of *Trypanosoma brucei* population dynamics in mice can test hypotheses for parasites growing in adipose tissue versus blood

Pham, Thi Mui

Tracking *P. aeruginosa* transmission routes in intensive-care units using mathematical models

Thursday, CS 7

Adamson, Matthew

Predicting resilience profiles of the run-up to regime shifts in nearly-1D systems

Legros, Mathieu

Gene drive strategies of pest control and resistance management in agriculture

Souza, Max

From fixation probabilities to d-player games: an inverse problem in evolutionary dynamics

Thursday, CS 8

delosReyes, Aurelio

STRATEGIES IN CONTROLLING GLIOBLASTOMA INVASION

MacKay, Vincent

Double-wave Reentry in Excitable Media

Osojnik, Ana

Systematic analysis of a bifurcating model of tumour-immune interactions

Thursday, CS 9

## Poster Sessions

**Monday**

1 Abboud, Candy	Model & data-based prediction of invasive species dynamics
2 Alkarkhi, Tahani	Stability analysis in prey predator model using BeddingtonDeAngelis functional response.
3 Althubyani, Mohammed	A two species model to study the transmission and persistence of MERS-COV
4 Andor, Noemi	Modeling the evolution of ploidy in a resource restricted environment
5 Ardaseva, Aleksandra	Analysis of cancer dynamics in fluctuating environments
6 Bajiyia, VijayPal	A Mathematical Model for Cholera Transmission: Most Effective Control Strategy
7 Baratchart, Etienne	Computational modeling of macrophage polarization dynamics during bone healing
8 Barendregt, Nicholas	Analyzing Dynamic Decision Models Using Differential Chapman-Kolmogorov Equations
9 Bayani, Anahita	Modelling the inflammatory response - spatial considerations in the resolution of inflammation
10 Bolohan, Noah	Seasonal Variation in a Predator-Predator-Prey Model
11 Brechman, Pia	Dynamics of the Selkov oscillator
12 Campbell, Kelly	A mathematical model of osteochondral defect regeneration
13 Chae, Seokjoo	Network inference of the circadian clock
14 Chavez, Luciana	How to incorporate genetic information into models for pesticide degradation in soils
15 Dengos, Isabel	Modeling the growth and sustainable control of invasive eurasian watermilfoil
16 Farahbakhsh, Isaiah	The evolution of strategies within a network harvesting common-pool resources
17 Fonseka, Dilini	The dynamics of stoichiometric plant-pollinator-herbivore models and parameter sensitivity analysis
18 Go, Clark Kendrick	Modelling the Herding of Garrano Horses in the Wild
19 Grosklos, Guen	The effects of metapopulation dispersal theory on Columbia spotted frog population dynamics
20 Halloway, Abdel	Non-Equilibrium Dynamics in Under-Saturated Communities
21 Hill, Edward	Seasonal influenza in England: Modelling approaches to capture immunity propagation
22 Hong, Jaehyoung	Analyzing the Sleep Patterns of Shift Workers using the neuronal population model of sleep-wake cycle
23 Hormuth, David A	Patient specific, predictive modeling of the response to chemoradiation via MRI
24 Inafuku, Daniel	Toward a new theory of biological information
25 Jansen, Joanneke E	Inference of an inflammatory cytokine interaction network
26 Jentsch, Peter	Fire Mediates Bark Beetle Outbreaks in Serotinous Forests
27 Johnson, Kaitlyn	An integrated approach to calibrate and validate mathematical models of therapy-induced resistance from <i>in vitro</i> drug response data in cancer
28 Kawakatsu, Mari	Self-organized division of labour leads to behavioural contagion in mixed social groups
29 Kelley, Michael	A mathematical model of thrombin-fibrin binding
30 Kim, Soyoung	Mathematical model and intervention strategies for mitigating tuberculosis in the Philippines
31 Kravtsova, Natalia	Modified Metropolis-Hastings Algorithm for Efficiently Searching Parameter Space
32 Lanz, Aprillya	An epidemic model of the spread of mobile phone malware with quarantine and removal classes

- 33 Lavigne, Michael  
 Upscaling Individual Based Models to PDEs with Equation Learning
- 34 Lehnert, Jonas  
 Modeling GnRH Neuronal Dynamics in Reponse to Kisspeptin Stimulation
- 35 Liu, Junyan  
 Development of an experiment-driven time-resolved model of response to radiation therapy
- 36 Loo, Sara  
 An evolutionary model of within-host mutation and between-host pathogen transmission
- 37 Makaryan, Sahak  
**MODELING THE STIMULATORY NETWORK IN NATURAL KILLER CELLS**
- 38 Martinson, Duncan  
 Applications of Multiscale Simulation Algorithms to Angiogenesis Models
- 39 Meyer, Alexander D  
 Sensitivity to larval settlement cues affects marine population viability
- 40 Minucci, Sarah B  
 Mathematical modeling of the role of macrophages in lung inflammation
- 41 Negelja, Rigobert C  
 Seasonal weather variation and the dynamics of infectious diseases
- 42 Oke, Segun  
 Mathematical Modeling of Breast Cancer and Optimal Control Analysis of Treatment Strategies
- 43 Olivencia, Daniel  
 Phosphoinositides and DGK control of the epithelial sodium channel in cystic fibrosis
- 44 Pak, Thomas  
 Pakman: a modular and efficient software tool for approximate Bayesian inference
- 45 Papaxenopoulou, Lito  
 Model-driven experiments induce elimination of *Staphylococcus aureus* chronic infection
- 46 Park, Daniel  
 Impact of adaptive myelination on synchrony in coupled oscillator networks
- 47 Pattenden, Tyler  
 Why fast-growing bacteria carry more DNA of viral origin
- 48 Patwardhan, Janita  
 $\beta$  cell network dysfunction in pancreatic islets by silencing hub cells
- 49 Pedersen, Rasmus  
 Modelling the Dynamics of Hematopoietic Stem Cells.
- 50 Pellowe, Moriah  
 A system biology approach to study anit-PD-1 cancer immunotherapy
- 51 Phillips, Brendon  
 Early-warning signals of epidemics in a multiplex disease-behaviour model
- 52 Rashid, Mubasher  
 Feedforward regulation of nitrate transporter NRT1.1 bi-functional activity depending on soil nitrate availabilities
- 53 Renton, Jessica  
 Evolution of cooperation on an epithelium
- 54 Rezzy, Eko Caraka  
 Zero-Inflated and Over-Dispersed Species Arthropods Count Data With Fast Estimation of GLLVM
- 55 Ridouan, Bani  
 Marine Metapopulation: Pelagic larval duration and ocean currents mediated effects of climate change
- 56 Roberts, Paul A  
 Using mathematics to investigate the mechanisms behind vision loss
- 57 Saha, Raj  
 Oscillation and Data in a Simple Epidemic Model
- 58 Schenck, Ryan O  
 The tick-tock of the molecular clock: A story from the crypt
- 59 Scott, Shelby  
 Handguns and Hotspots: Spatio-Temporal Models of Gun Crime in Chicago, Illinois
- 60 Smith-Roberge, Julien  
 Effects of alignment on contact dependent cell-cell interactions
- 61 Strobl, Maximilian  
 Man vs Machine: in silico and in vitro comparison of a mechanistic and a machine learning model for guiding cancer treatment
- 62 Susswein, Zachary  
 Borrowing ecological theory to infer interactions between sensitive and resistant cancer cell populations
- 63 Walton, Jack  
 Inferring collective behaviour rules from field data

64 Wang, Wendy	Dynamics of a state dependent delay model of the tryptophan operon
65 Yang, Jianchen	Modeling the effect of glucose availability on tumor cell growth guided by in vitro microscopy
66 Zahid, Mondal H	Ebola: Impact of hospital's admission policy in an overwhelmed scenario
67 Zou, YiMing	Integrated Analysis of Gene Regulatory Networks

## Tuesday

1 Amoah-Darko, Frederick L.	Continuous model of dynamics instability of microtubules with pausing
2 Aruffo, Elena	Measles: Insights into waning immunity
3 Ballif, Guillaume	An application of spatial stochastic interacting systems on multiple time scales to biological systems
4 Bashir, Umar	USING MATHEMATICAL MODEL TO ASSESS THE IMPACT OF VACCINATION OF MEASLES
5 Betti, Matthew	The transfer of honey bee disease in heterogeneous landscapes
6 Beykzadeh, Ali	A matrix form of the general Laplace kernel
7 Brindle, Benjamin	The Mathematical Role of Immunity on the Within-Host Malaria Parasite Dynamics
8 Bury, Thomas	Spectral early warning signals improve tipping point detection and description
9 Choi, Wonhyung	Evolution of dispersal toward fitness for predators with predation-induced dispersal
10 Chu, Olivia	Evolutionary Dynamics in a Group Population Structure with Barriers to Entry
11 Cooney, Daniel	THE REPLICATOR DYNAMICS FOR MULTILEVEL SELECTION IN EVOLUTIONARY GAMES
12 Cresswell, Evan	Compartmental modeling of calcium dynamics in astrocytes
13 Dam, Marc JB	Comparing efficacy of hydroxyurea and IFN- $\alpha$ treatment in MPN patients
14 Dang, Yiteng	Cellular dialogues that enable self-organization of dynamic spatial patterns
15 Das, Parthasaratha	Noise Assisted Extinction of Chaotic Cancer Model
16 Davis, Jacob	Metrics for regulated biological systems
17 Dobrovolny, Hana M	Oncolytic virus treatment of cancer
18 Fair, Kathryn	Spatially explicit models simulate rich forest-grassland mosaics
19 Flores, Pavel	Networks provided from neuronal activity
20 Geng, Yunfeng	The coexistence of competing consumers on a single resource in a hybrid model
21 Giniunaite, Rasa	Investigating the effect of domain growth on the collective migration of neural crest cells
22 Gunaratne, Ravinda	MUTLI-RESOLUTION MODELLING IN MOLECULAR DYNAMICS
23 Herrera-Reyes, Alejandra D	Identifying unique observations dSTORM with a spatiotemporal model
24 Hong, Hyukpyo	Product-Form Stationary Distributions for Non-Complex Balanced Networks
25 Jeong, Eui Min	Mathematical Modeling to Reveal Molecular Differences Causing Pacemaker-neuron-dependent Rhythm Alteration by Mutant
26 Katebi, Ataur	Dynamics of gene regulatory circuits drive irreversible transition of cell cycle

- 27 Khan, Amjad  
The evolutionary forces acting on prophages: A mathematical study
- 28 Khataee, Hamid  
Force-dependent mechanics of kinesin molecular motors
- 29 Kramer, Sean  
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# Abstracts

## Coming Full Circle in Cancer Modelling?

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The past twenty five years have been marked by an unparalleled increase in our understanding of cancer biology. This transformation is, perhaps, best exemplified by Hanahan and Weinberg's decision in 2011 to expand their original Hallmarks of Cancer from six traits to ten! At the same time, mathematical modelling has emerged as a natural tool for unravelling the complex processes that contribute to cancer initiation and progression, for testing hypotheses about experimental and clinical observations, and assisting with the development of new approaches for improving its treatment.

In this talk, I will revisit some of the early models of avascular tumour growth, angiogenesis and tumour blood flow. Following Hanahan and Weinberg's lead, I will reflect on how closer collaboration with oncologists and access to experimental data have driven extensions to these models which increase their power to generate qualitative and quantitative predictions about the growth and response to treatment of solid tumours.

## Mathematical models, genomic data and prediction in infectious disease

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It is now possible to gather rich, high-resolution datasets describing the diversification of infectious pathogens. In many settings, pathogens are able to evade interventions like vaccination and antibiotic treatment by evolving vaccine escape strains, acquiring antimicrobial resistance or through ecological competition. The ability of pathogens to evolve on relatively short time scales is undermining our ability to control a range of infectious diseases. Mathematical models have a key role to play in understanding this evolution, and models can help us to design interventions that mitigate evolutions' effects, at least temporarily. In this talk I will describe models that are implicitly or explicitly driven by questions in diverse pathogens, and show how they can be used to aid in the design of interventions. In *Streptococcus pneumoniae*, I will present a model that builds on an empirical principle observed in large-scale genomic data, and uses that principle to design optimized vaccine formulations producing a (predicted) “benign” post-vaccine bacterial population. In influenza, I will present a machine learning approach to predict the short-term success of small influenza virus subtrees using a large influenza virus HA phylogeny. In both cases, models can be built, tested, and refined using large-scale genomic data. The results can, in principle, be used to improve our interventions. Most genomic analyses have been primarily retrospective in nature – in contrast, we now have the opportunity to use genomics and modelling together to move from retrospective analyses towards prediction.

# Novel Physiological Mechanisms Revealed Through Mechanistic Modelling of Granulopoiesis Guides the Optimization of Chemotherapy Regimens

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Neutrophils are the most abundant white blood cells in the body and are front-line defenders against bacterial and fungal pathogens. As a lack of neutrophils leaves individuals open to serious infections that could comprise their health, low neutrophil counts (neutropenia) are especially concerning to clinicians. Terminal blood cells are produced from hematopoietic stem cells (HSC) in a variety of processes mediated by a host of small proteins called cytokines. The production of neutrophils occurs primarily through negative feedback with the cytokine granulocyte colony-stimulating factor (G-CSF), so that when neutrophil counts are high, G-CSF concentrations are low and vice versa.

Unfortunately, patients undergoing chemotherapy are particularly subject to periods of acquired neutropenia due to the indiscriminate nature of cytotoxic chemotherapeutic drugs. A lack of neutrophils during chemotherapy often necessitates dose adjustments and/or complete therapy cessation until neutrophil counts recover, which severely hampers the effectiveness of the treatment. In response, exogenous G-CSF is frequently co-administered with chemotherapy in hopes of staving off neutropenic periods. Unfortunately, the timing of combination G-CSF/chemotherapy remains an open problem, despite granulopoiesis being the subject of many mathematical biology and pharmacometric models.

Here I will detail the construction of a novel physiological model of neutrophil production from HSCs that incorporates detailed pharmacokinetic/pharmacodynamic (PK/PD) considerations. I will show how traditional PK approaches have previously mischaracterized the elimination kinetics of G-CSF, leading to erroneous parameter estimates and a misunderstanding of how G-CSF is removed from the body. I will also outline how our physiological model can be leveraged to tailor combination chemotherapy/G-CSF regimens by determining the optimal timing of G-CSF administration during cytotoxic chemotherapy. The resulting optimized regimens offer significant insight into the fundamental mechanisms regulating neutrophil production, and, most importantly, demonstrate concrete benefits to patient outcomes.

## Transients, autocorrelated variation, and invasive species impact

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Common approaches for estimating invasive species risk focus on asymptotic conditions. For example, niche-based or correlation models use average climate conditions to predict whether species will persist indefinitely in a new location. While these models are useful for understanding persistence, they may underestimate risk of impact. I review two previous studies where impact is more likely to be related to probability of exceeding a threshold population size given an initial stage distribution (Asian carps), or probability of exceeding a persistence time in a variable environment (Emerald ash borer). The mathematical methods we used to estimate these risks deal with transient states.

A major issue for modeling newly introduced populations is that they are far from an equilibrium stage distribution (e.g., the proportion of juveniles and adults). This unstable-stage structure can cause transient dynamics that differ from the long-term dynamics. However, transient dynamics are also affected by environmental variation, which is usually autocorrelated.

In a simple unstructured population model, autocorrelated variation, incorporated in the per capita population growth rate as a  $1/f^\beta$  process, increases the probability that newly introduced populations temporarily reach extremely high densities, whereas uncorrelated variation decreases the maximum predicted population size. That is, autocorrelated variation alters our expectation regarding the effects of stochasticity on the transient dynamics of populations.

I synthesize these ideas about transient dynamics and invasive species by focusing on structured models of invertebrate populations. Invertebrates can be introduced at various life stages, have vital rates tightly coupled to environmental conditions, and include some of the most invasive species. I find that unstable stage structure associated with recent introduction, and autocorrelated temporal variation that affects vital rates, can produce transients with large growth rates in structured population models. Therefore, there is a possibility of large ecological or economic impact of newly introduced species even when minimal risks are predicted by the asymptotic growth rates.

# Evolutionary dynamics of cancer: from epigenetic regulation to cell population dynamics

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**Abstract** Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. Cancer development is a long-term process which remains mostly unknown; predictive modeling of the evolutionary dynamics of cancer is one of the major challenges in computational cancer biology. In this talk, I introduce a general mathematical framework for understanding the behavior of heterogeneous stem cell regeneration, and the application of the model framework to study the evolutionary dynamics of cancer. The proposed model framework generalizes the classical G0 cell cycle model, incorporates the epigenetic states of stem cells that are represented by a continuous multidimensional variable, and the kinetic rates of cell behaviors, including proliferation, differentiation, and apoptosis, which are dependent on their epigenetic states. The random transition of epigenetic states is represented by an inheritance probability that can be described as a conditional beta distribution. Moreover, the model framework can be extended to investigate gene mutation-induced tumor development. The model equation further suggests a numerical scheme of multi-scale modeling for tissue growth where a multiple cell system is represented by a collection of epigenetic states in each cell. We applied the numerical scheme to model the two processes of inflammation-induced tumorigenesis and tumor relapse after CD19 chimeric antigen receptor(CAR) T cell therapy of acute B lymphoblastic leukemia (B-ALL). Model simulations reveal the multiple pathways of inflammation-induced tumorigenesis, and the a mechanism of tumor relapse due to leukemic cell plasticity induced by CAR-T therapy stress.

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## Rules of Life in the Context of Future Math Biology

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Understanding the Rules of Life is one of NSF's Big Ten Ideas. New techniques and approaches in mathematical sciences are needed to uncover and analyze fundamental rules governing biological systems. This interactive panel is intended to spark discussion on the future of research in mathematical biology, and is the continuation of a charrette held in November, 2018. This session will consist of three parts: 1) an overview of the November 2018 meeting and community-proposed areas of research importance (led by Seshaiyer, Eisenberg and Dawes) 2) NSF programs and opportunities surrounding the Rules of Life (presented by NSF Division of Mathematical Sciences program officers Jim Powell and Junping Wang), and 3) an open discussion to broaden involvement of the math biology community. For those who wish to get further involved, information about organization of future related meetings and aiding in the generation of white papers will be provided.

# Network dynamics: Epidemic processes and energy landscape analysis

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In this presentation, I present two topics centered around dynamics of networks.

The first topic is epidemic processes on temporal (i.e., temporally varying) networks. While contact networks are often dynamical constructs, the understanding of and intervention in epidemic processes in temporal networks are complicated by complexity of both network structure and temporal dimensions. We analyze the susceptible-infected-susceptible (SIS) epidemic model on a type of temporal networks. We evaluate the epidemic threshold for the temporal network in an explicit comparison with that for the corresponding static network, using both deterministic and stochastic approaches, each of which is valid in different regimes of contact density. In the course of analysis, we highlight the effects of concurrency (i.e., the number of neighbors that a node has at a given time point) on the epidemic threshold. In particular, we show that network dynamics can suppress epidemics (i.e., yield a higher epidemic threshold) when nodes' concurrency is low (where stochasticity effects are stronger) and can enhance epidemics when the concurrency is high.

The second topic is the so-called energy landscape analysis, which is a method for analyzing multivariate time series data. With this analysis, one identifies the state of the system at each time point as the position of a “ball” constrained on an energy landscape inferred from data. A ball tends to go downhill on the energy landscape, whereas it sometimes goes uphill to transit from one local minimum of the energy to another, possibly corresponding to major dynamical transitions. The method is based on the Ising model (also known as Boltzmann machine). The application of the method to neuroimaging data is illustrated. The method may be useful for analyzing various types of multivariate temporal data in mathematical biology, such as collective dynamics of animal individuals and time courses of interacting gene regulation.

## Mathematical Modelling in Biology: Integration and Differentiation

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Mathematical modelling in biology occupies a liminal space between mathematics and biology. It is rich with opportunity, but not without its challenges. A key question is that of identity: is the subject a sub-discipline of mathematics, of biology, or something separate? To whom, and how, should it be taught? And at what stage? As modelling in biology matures, these questions become more pressing. We are no longer a small band of pioneers forging a new discipline; modelling increasingly plays a central role in biological research. So how can we best go about the task of training the next generation of mathematicians/biologists? Integration is key: modelling has to be seen as a standard approach in biology. But differentiation also needs to be maintained: the particular contribution of well-trained and experienced mathematicians and statisticians needs to be appreciated and recognised. I will present my experiences of teaching mathematical biology in a range of contexts in the light of these questions.

## Type 2 Diabetes: New Equations, New Thinking

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Insulin is the chief hormone that regulates glucose homeostasis, preserving glucose for use by the brain in fasting conditions but sharing glucose with other tissues, such as muscle, after meals. This orderly cycle of fuel usage is disrupted in obesity, which renders tissues resistant to the effects of insulin and leads to chronic hyperglycemia, a condition known as type 2 diabetes. A salient characteristic of diabetes is its relentless progressive nature, which is almost impossible to reverse once the disease is established and difficult to reverse in the pre-diabetes stage when glucose is elevated but below the diagnostic threshold. Proper understanding of this process for diagnosis and treatment requires a longitudinal mathematical model. Furthermore, because different organs play the dominant roles in fasting conditions (the liver) and fed conditions (muscle), the pathway to diabetes varies widely across individuals, with some showing elevation first in fasting glucose and others first in post-prandial glucose. The pathways differ as well systematically among age groups (e.g., adolescents vs adults) and ethnic groups. These distinct pathologies, which optimally require different therapies, can be probed in a standardized way by administering an oral glucose tolerance test (OGTT), a two-hour glucose challenge. We show by simulation of OGTTs sequentially over a period of years that properly targeted therapies are more effective than mistargeted ones. We also shed light on a current controversy about whether glucose at the one hour or at two hour time point of an OGTT is better for defining pre-diabetes. We take advantage of a rare longitudinal clinical study of Pima Indians in Arizona to show that one-hour glucose crosses its threshold before two-hour glucose, potentially providing a two-year lead time in initiation of treatment. The model predicts that the difference between one-hour and two-hour glucose contains valuable information about the relative contributions of impaired insulin secretion and insulin resistance and is characteristic of ethnicity. Finally, whereas the established diagnostic threshold values of glucose are based on statistical associations with the complications of diabetes, such as vision loss and kidney failure, the model argues that diabetes onset is a true threshold crossing between bistable states of health and disease. However, the true threshold is different for each individual and may be better assessed by tests simpler than the OGTT that can be done frequently to track the trajectory of each person's glucose levels.

## Toward a Quantification of Atherosclerosis

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There are a growing number of studies that model immunological processes in the artery wall that lead to the development of atherosclerotic plaques. However, few of these models use parameters that are obtained from experimental data even though data-driven models are vital if mathematical models are to become clinically relevant. In this contribution, we present a quantitative ODE model for the coupled inflammatory, lipid and macrophage dynamics in early atherosclerotic plaques that is parameterized using data from existing in vitro experiments. The modeling approach that is presented is similar to the biologists' experimental approach where the bigger picture of atherosclerosis is put together from many smaller observations and findings from in vitro experiments. The model suggests future experimental work and allows the classification of the long-term stability of early atherosclerotic plaques from their rates of recruitment of low-density lipoproteins, high-density lipoproteins and macrophages. It is an important step toward a quantification of atherosclerosis and models that are applicable in a clinical setting.

Message in a bottleneck:  
How transmission bottlenecks shape the evolution of influenza and HIV.

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Many viral infections are characterized by a severe in-host viral burden, that is, the viral population within an infected individual peaks at very high concentrations. Between individuals, in contrast, new infections can be transmitted by one or a handful of infectious viral particles. Using influenza A and HIV as examples, I will describe our recent work in characterizing the effects of these transmission bottlenecks on viral evolution. In both cases, we couple a deterministic in-host model with stochastic transmission between hosts. This approach allows us to predict how transmission bottlenecks have historically slowed the evolution of HIV, and to shed light on the “source-sink” hypothesis of influenza transmission dynamics.

# Mathematical Assessment of the Role of Temperature and Rainfall on Multi-Species Interactions in West Nile virus

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Extrinsic factors such as temperature and rainfall use are determinants of West Nile virus (WNv) outbreaks in North America, along with intrinsic factors of the vector and virus. In this paper, a new non-autonomous model is designed and used to study the effect of variability in temperature and rainfall on the dynamics of WNv transmission. Furthermore, we analyse the interaction of different species of birds, mammals and mosquitoes on the dynamics of WNv infection

## Extinction is (almost) inevitable: Why cancer is rare

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Recent detailed study of cells in adults shows that few if any cells are actually “normal.” Instead, any renewing tissue is made up of lineages with increasing numbers of aberrant traits, many of which are associated with excess growth. Nonetheless, these lineages, whether in the primary tissue or at sites of metastasis, are almost always doomed to extinction by a wide range of controls both within the cell and in their microenvironment.

I present a modeling framework to address the continual emergence, control and extinction of abnormal cells, and analyze the time course of these dynamics with different subsets of controls in place. In particular, I contrast this process with a more ecological scenario where regulatory mechanisms are restricted to competition for resources, natural enemies and behavioral controls. The finely-tuned set of physiological controls creates rare but catastrophic outbreaks of cancer rather than the messy but more tolerant regulation of native species and the typical exclusion of exotic invaders.

# Large Deviations for Strongly Endotactic Chemical Reaction Networks

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The dynamics of networks of chemical reactions can be modeled, at the microscopic level, as jump Markov processes whose sample paths converge, in the limit of large number of molecules, to the solutions of a set of algebraic ordinary differential equations. Fluctuations around these asymptotic trajectories can in principle be studied through large deviations theory in path space, also called Wentzell-Freidlin (W-F) theory. However, the standard regularity assumptions imposed by that theory are not satisfied by the processes under consideration, and weaker conditions need to be developed to deal with the framework at hand. After introducing the class of models under investigation and the formulation of some relevant theorems in W-F theory, in this talk I will outline sufficient conditions that allow to apply this theory to the class of models at hand. Translating such conditions in terms of the topological structure of the chemical reaction network, I will then define a large class of chemical reaction systems to which such estimates can automatically be applied.

# Impact of Regional Movement on Methicillin-resistant *Staphylococcus Aureus* among Injection Drug Users

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In this seminar, I will present a deterministic model for methicillin-resistant staphylococcus *aureus* (MRSA) among injection drug users. The model incorporates transmission of the bacterial among non-injection drug users and injection drug users (IDUs) who are both low-and high-risk users, and their movement between large metro, sub-urban and rural areas.

The model parameters are fitted using disease prevalence data from 2008-2013 obtained for non-IDUs from the Agency for Healthcare and Research and Quality (AHRQ). Sensitivity analysis was implemented to determine the parameters with the most significant impact on the total number of infected individuals; the transmission probability and recovery rates for the subgroup were found to have the highest impact on the number of infected individuals. Furthermore, the sensitivity of the parameters in the different areas was the same when the areas are disconnected. When they are connected, the parameters in large-metro areas were more sensitive, and the rural areas were least sensitive.

The result shows that to effectively control the disease across the large metro, suburban and rural areas, it is best to focus on managing both behavior and disease in the large metro area as this have a trickle-down effect to the other places. Controlling behavior and disease at the same time in all the regions will lead to the elimination of the disease.

## Stochastic Epidemic Model for Zoonotic Spillover

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It is estimated that over 60% of human infectious diseases are zoonotic, spread from animals to humans. Many emerging and re-emerging zoonotic diseases are of viral origin such as avian influenza, rabies, Ebola, and orthohantaviruses. Spillover of disease from animal to humans depends primarily on the contact between animals and humans. Environmental factors, such as seasonal variations in temperature, humidity, or rainfall, also impact the spread of zoonotic diseases. In this investigation, a nonhomogenous stochastic process is formulated for zoonotic disease spread from animals to humans, based on susceptible-infectious-recovered epidemic modeling for animals and humans. A branching process approximation allows estimation of the probability of the first spillover event from animal to human after the animal population is initially infected. When the animal recovery rate and the transmission rates among animals and from animals-to-humans are assumed to vary seasonally, then it is shown that the probability of spillover also varies seasonally. However, it is discovered that the highest risk of the first spillover event does not coincide with the peak value of the animal-to-human transmission. Examples to rabies and orthohantavirus outbreaks are discussed.

# Mathematical Modeling to Support Discovery and Development of Therapies for NASH and other Chronic Inflammatory Diseases

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To support the discovery and development of therapies for inflammatory diseases we are building models of the patho-physiological progression of disease, and ultimately treatment. An example of our approach is our models of Non-Alcoholic Steatohepatitis (NASH), which is a chronic condition with metabolic and inflammatory components. The initial insult in NASH is the ectopic accumulation of fat in the liver, which in some patients leads to a hepatic inflammatory response and fibrosis.

Here we will present ordinary differential equation models which capture the metabolic insult and its treatment, and then a continuous-time markov chain model of progression of fibrosis in clinical cohorts. We will describe our strategy to link these via inflammatory models. We will also describe the broader perspective of our strategy of supporting drug discovery and development with mathematical models in general, and for inflammatory conditions.

## Biomechanics of Intestinal Crypt Morphogenesis

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The intestinal epithelium exhibits remarkable rates of self-renewal to protect the small intestine and colon during digestion and facilitate nutrient absorption. This monolayer of epithelial cells is maintained by the crypts of Lieberkühn, test-tube-shaped glands that are robust in morphology and structure, undergoing significantly large deformations, despite comprising a heterogeneous composition of cells with varying proliferative capacities and mechanical properties. While the genetic and molecular processes governing crypt morphogenesis have been studied in detail, there is a lack of understanding regarding the evident contribution of biomechanical factors, leading to a poor understanding of crypt morphogenesis as a whole. In this talk, I present a mathematical model of a growing intestinal crypt, using the framework of morphoelastic rods, which extends the classical Kirchhoff rod theory to account for local tissue growth. I will show how morphogenesis can be modelled through the buckling and subsequent large deformation of an elastic rod (the row of proliferating epithelial cells) tethered to an underlying foundation, representing the crypt and the supporting extracellular matrix and stroma. We then consider how best to incorporate various mechanical, chemical, and biological processes, from the subcellular to the tissue scale. Simulation results demonstrate the relative importance of each modelled component to the morphology and properties of the crypt, and how different assumptions can lead to significantly different emergent behaviours. Time permitting, I will also discuss recent work comparing this continuum framework to discrete, cell-based models of the crypt.

# An agent-based model of host response to infection as a proxy system for control discovery using evolutionary computation and game-playing Artificial Intelligence

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Sepsis, which is brought about by the body's host response to severe infection or injury, is one of the most prevalent causes of mortality in intensive care units (ICUs). Sepsis has a mortality rate of 30-40% and a cost of more than \$20 billion annually in the US. The fundamentals of sepsis care, antibiotics, fluid management and organ support, have not changed in nearly 30 years, and to date there is no single approved drug that targets the pathophysiological processes that drive the host-response that produces sepsis, this despite tens of billions of dollars spent on hundreds of failed clinical trials. We have proposed that the controllability of sepsis can be examined by using a previously validated agent-based model (ABM) of the host response to infection as a proxy model upon which different methods of control discovery have been applied. Specifically, we treat the search for an effective multi-modal treatment regimen as a control-optimization problem that manipulates the internal variables of the ABM with combinations of putative molecular-based interventions at different intervals. Given the combinatorial complexity of the high-dimensional potential control space we have applied both genetic algorithms and deep reinforcement learning (as used in the game-playing DeepMind artificial intelligence systems, e.g. AlphaGo and AlphaZero) to characterize the scale of the control problem. Implemented on high-performance computing environments and following the principle that clinical heterogeneity is a function of model parameter space, both approaches produced fairly generalizable solutions, but with acknowledged limitations in interpretability and potential clinical translation. We suggest that these technologies can be integrated with ABM development in an iterative workflow that can both continually refine the ABM as well as guide basic and translational research in sensor and drug design. This approach for multi-scale model-based control discovery is potentially applicable to any complex disease process.

# Hematopoiesis or inflammation driven blood cancer? Insights from mathematical modelling

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We develop and investigate a mathematical model of the blood cancer type Philadelphia-negative myeloproliferative neoplasms (MPNs) [1]. The MPNs have a low incidence but a prevalence as lung cancer, since most MPN patients live with their MPNs for decades although with an increased morbidity burden due to a high risk of thrombosis and an increased propensity to develop autoimmune and chronic inflammatory diseases. Chronic inflammation is today considered to be a highly important patogenetic factor for the development of MPNs both as a trigger and a driver of clonal evolution. Several years prior to the typical MPN-diagnosis the patients also have an increased risk of cardiovascular, autoimmune and inflammatory diseases. During the last decade major breakthroughs have occurred in the understanding of the pathogenesis of the MPNs, the most important being the identification of the somatic clonal markers JAK2, MPL and CALR.

The model includes healthy and cancerous stem cells and mature cells and the innate immune response including inflammatory load. Due to several feedback signals e.g. stem cell niche interaction, and cytokine feedback on the stem cell dynamics, the governing differential equations are nonlinear. Parameters are estimated from the literature and from clinical data. Due to a time scale separation of the governing equations, we then investigate a new reduced model with only two dynamic variables and four algebraic equations which approximate the original model very well. Results of the reduced models comprise 1) Formulation of identifiable, new parameters being combinations of the original parameters of the problem. 2) Dynamical variables accessible in typical, clinical measurements. 3) The reduction to two dimensions allows for a complete mathematical investigation of steady states and their stability. We provide conditions for a globally stable healthy state, MPN state or coexisting state with low number of cancerous cells. An approximate, closed form solution is derived. The results are compared to clinical data and implications for treatment strategies are discussed.

## References

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# Stochastic Chemical Reaction Networks for Robustly Approximating Arbitrary Probability Distributions

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We show that discrete distributions on the d-dimensional non-negative integer lattice can be approximated arbitrarily well via the marginals of stationary distributions for various classes of stochastic chemical reaction networks. We begin by providing a class of detailed balanced networks and prove that they can approximate any discrete distribution to any desired accuracy. However, these detailed balanced constructions rely on the ability to initialize a system precisely, and are therefore susceptible to perturbations in the initial conditions. We therefore provide another construction based on the ability to approximate point mass distributions and prove that this construction is capable of approximating arbitrary discrete distributions for any choice of initial condition. In particular, the developed models are ergodic, so their limit distributions are robust to a finite number of perturbations over time in the counts of molecules.

# Heterogeneity in the longevity of immunological memory in humans

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We characterize the extent of this heterogeneity and determine how it affects the longevity of protection. We find that some individuals have higher antibody titers and these same individuals tend to have slower decay rates than others. We also found substantial heterogeneity in both the magnitude and decay rate of responses. Furthermore, differences in these two factors contribute comparably to the variation in antibody titers between different individuals over their lifetime. We use statistical models to determine how variation in the magnitude and decay rate affect how protective immunity is lost at the population level to different virus and vaccine antigens and identify different patterns for the loss of protective immunity elicited by protein immunization (tetanus and diphtheria) versus replicating viruses (measles, rubella, and vaccinia).

## Dissecting drug action and host responses during malaria infection

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Malaria still remains a major health problem across the globe. Currently, antimalarial drugs are the most commonly used intervention which has contributed to the reduction in mortality and morbidity caused by malaria infection. However, the rise in drug resistance of the major human species *Plasmodium falciparum* threatens this progress. Therefore, there is a critical need for new antimalarial drugs and an effective vaccine. Successful interventions, whether vaccines or drugs, must control infection. This could involve the direct removal of circulating parasites and/or blockage of new infections. I will discuss a range of projects in which we have sought to understand how parasites survive in an infected host, and how various immune and antimalarial interventions lead to control of infection.

We utilise data from an established *murine model* that tracks the loss of a single cohort of infected RBCs and development of parasites through their lifecycle both *in vivo* and *in vitro* and combined this with mathematical modelling to understand how a variety of host or therapeutic interventions control infection. We first developed a modelling approach that directly estimates the host rate of parasite removal and separately estimated the average progeny of each infected cell. We also utilized age-structured PDE models to analyse experimental data in order to estimate the rate of parasite development. We applied these experimental and mathematical methods to understand how different drugs act against parasites, to explore the role of key parasite proteins in parasite survival in the host, and the impact of host immune responses on parasite survival.

A key insight from this work has been identifying that the rate of parasite clearance cannot easily be improved from the basal rate by drug treatment or host responses. In fact, most control of infection by treatment or host responses targets parasites by killing or impairing their development, or targeting parasites when they are outside RBCs. Also, we identified that a key parasite protein, responsible for transporting other parasite proteins to the surface of the red blood cell, is not required for parasites to avoid clearance or to produce progeny, but is important in regulating the time it takes parasites to develop and produce progeny. Collectively, our work greatly improves our understanding of host and parasite interactions in malaria infection that govern parasite survival and control of infection.

## ON THE DURATION OF THE STOCHASTIC PHASE OF AN EPIDEMIC

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Before they “explode” into full blown epidemics or they go extinct, infectious diseases go through an initial phase during which the number of cases evolves in a seemingly random way. Call *stochastic* this initial phase. Our aim here is to study the duration of this stochastic period. To do so, we formulate a simple Markov chain model with two absorbing states: disease extinction or full blown epidemic. We study this chain using classic and more advanced method. We then formulate an equivalent model for the spread between spatially distinct locations and evaluate the effect of this on the duration of the stochastic phase.

## How ageing and disease affect hematopoietic stem cell dynamics

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The hematopoietic stem cell (HSC) pool expands over a lifetime, as well as during diseases such as MPN. However, there is disagreement as to what physiologic changes HSCs go through during these periods. Here we combine population dynamics models and *in vivo* proliferation label experiments to infer the parameters describing HSC division, differentiation, and quiescence dynamics. We find that accounting for cell cycle status has a significant impact on how the results are interpreted, and this is a cautionary tale in data handling! Through this, we hope to settle the debate surrounding hematopoietic stem cell dynamics, and to understand the physiologic impact that ageing and disease have at the single-cell level.

## Environmental Seasonality on Predator-Prey Systems Under Nutrient and Toxicant Constraints

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Environmental toxicants such as chemicals, heavy metals, and pesticides and environmental fluctuations are important factors influencing real aquatic ecosystems. Therefore, the investigation of the role of these factors in aquatic population dynamics is important. In this study, we extend an existing model for a toxin-dependent predator-prey model that incorporates variable food quantity as well as quality to better understand the role of seasonally varying carrying capacity on population dynamics. In the absence of seasonal effects, previous models suggest that the dynamics include Hopf bifurcation, saddle-node bifurcation, and limit cycles. However, seasonal effects can have major implications on the predicted solutions and enrich population dynamics. Bifurcation analyses demonstrate that seasonal forcing can cause periodic and quasi-periodic solutions.

## Testing Models of mRNA Localization Reveals Robustness Regulated by Reducing Transport between Cells

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Robust control of gene expression in both space and time is of central importance in the regulation of cellular processes, and for multicellular development. However, the mechanisms by which robustness is achieved are generally not identified or well understood. For example, mRNA localization by molecular-motor-driven transport is crucial for cell polarization in numerous contexts, but the regulatory mechanisms that enable this process to take place in the face of noise or significant perturbations are not fully understood. Here we use a combined experimental-theoretical approach to characterize the robustness of gurken/TGF-alpha mRNA localization in Drosophila egg chambers, where the oocyte and 15 surrounding nurse cells are connected in a stereotypic network via intracellular bridges known as ring canals. We construct a mathematical model that encodes simplified descriptions of the range of steps involved in mRNA localization, including production and transport between and within cells until the final destination in the oocyte. Using Bayesian inference, we calibrate this model using quantitative single molecule fluorescence *in situ* hybridization data. By analyzing both the steady state and dynamic behaviours of the model, we provide estimates for the rates of different steps of the localization process, as well as the extent of directional bias in transport through the ring canals. The model predicts that mRNA synthesis and transport must be tightly balanced to maintain robustness, a prediction which we tested experimentally using an over-expression mutant. Surprisingly, the over-expression mutant fails to display the anticipated degree of overaccumulation of mRNA in the oocyte predicted by the model. Through careful model-based analysis of quantitative data from the over-expression mutant we show evidence of saturation of transport of mRNA through ring canals. We conclude that this saturation engenders robustness of the localization process, in the face of significant variation in the levels of mRNA synthesis.

# Data-driven brain network models differentiate individual cognitive variability

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Structural connectivity is believed to be the foundation on which functional brain dynamics emerge. In our work, we investigate the relationship between functional and structural connectivity of the human brain, and how well they can explain and predict individual differences in cognition. To capture structural variability, we built computational models that combined individual structural connectivity derived from diffusion imaging with nonlinear Wilson-Cowan oscillators to represent the spatiotemporal dynamics of brain activity. These personalized models allowed us to explore the functional effects of naturally occurring structural differences in brain networks. Using these models, we showed that the performance on some language-demanding tasks can be correlated with either local or global network features, depending on the complexity of the task [Bansal et al. Plos Comp. Biol. 2018]. We also used these models to study the effect of regional stimulation by analyzing the global organization of emergent synchrony patterns within a cognitively-defined framework. Our results identified the impact of subject-specific and region-specific structural variability on brain dynamics [Bansal et al. Sci. Adv. 2019]. In our ongoing work, we are investigating the functional patterns of synchrony within the brain networks that emerge during the performance of different cognitive tasks. Collectively, our approaches serve as a powerful framework to assess individual differences in cognitive task performance.

## Study of the effect of individual cell behaviors on prion protein aggregation and propagation in yeast

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Prion proteins are most commonly associated with fatal neurodegenerative diseases in mammals, but they are also responsible for a number of harmless heritable phenotypes in yeast. The diseased state (or phenotype) in yeast arises when a misfolded form of a protein, i.e. prion, appears and, rather than be removed by cellular quality control mechanisms, persists. Mathematical models have previously been developed for studying prion aggregate dynamics in isolation. However, a major open question in prion biology is to understand how prion aggregates spread between cells within a whole colony or tissue. Living cells are constantly going through different behaviors such as growth, diffusion, and division, that impact the abundance and concentration of normal proteins and aggregates. These behaviors are thought to have a large impact on prion protein aggregation and propagation.

We introduce a novel, two-dimensional agent-based model of a budding yeast colony with detailed representation of cell-type specific biological processes, including budding, variation in cell-cycle length, and asymmetric protein segregation. The model is used to study how individual cell behaviors impact protein aggregation and propagation in an entire yeast colony. In the model, prion dynamics are simulated within each individual cell using simplified intracellular dynamics. In addition, spatial arrangement of cells is modeled using a center-based modeling approach that accounts for the affect of biophysical properties such as increased adhesion between a mother and daughter cell during budding. The unified model may have the potential to predict mechanisms underlying experimentally observed phenomena such as sectored prion phenotypes in yeast colonies in addition to serving as a tool for future hypothesis generation and testing.

## Analyzing the inflammatory response to a bacterial infection in rats

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Sepsis is a serious health condition defined by an overactive immune response that causes severe damage to healthy tissue, often resulting in death. Mathematical modeling has emerged as a useful tool to investigate key elements of the immune response and thus offers a useful method for studying sepsis. Here, a system of four ordinary differential equations is developed to simulate the dynamics of bacteria, the pro-inflammatory immune response, anti-inflammatory immune response, and tissue damage. The model is used to assess the conditions under which health, aseptic (inflammation-driven) death, or septic (bacteria-driven) death is predicted in both the presence and absence of an induced E. Coli bacterial infection in rats. Model parameters are fit to experimental data from rat sepsis studies. The model is used to predict the survivability range for an infection while varying the initial amount, growth rate, or virulence of the bacteria in the system. For highly virulent strains of bacteria, aseptic or septic death is predicted for very small levels of initial bacterial loads. Model predictions are also used to explain the experimentally observed variability in the mortality rates among rats.

# A Matrix Population Forecasting Model for *Aedes aegypti* Considering Daily Weather and Its Impact over the Dormancy State

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Stage-structured matrix population models are useful to investigate population dynamics, and have been successfully applied to vector modeling. To construct this type of model, one considers that the matrix blocks correspond to biological processes which allow building a bridge from the level of the individual to the whole population. With this propose, we develop a model to investigate the behavior of *Aedes aegypti* population dynamics and to estimate its abundance for Brazilian municipalities. There are four stages, corresponding to the quiescence and nonquiescence eggs, the aquatic development (larva and pupa) and the female adult mosquito. Each coordinate of the mosquito vector represents the number of individuals in the current stage over the same age. We consider a population projection matrix, composed by oviposition, transitions, and mortalities functions, which depend on the daily mean or accumulated temperature, the individual age and the daily or accumulated precipitation. There is an associated sparse matrix governing the system for each time. Due to its structure, when we set constant weather conditions, we are able to evaluate stability by calculating the net reproductive value. We point out that the use of temperature and precipitation, together with the quiescence approach, make it possible to study the development and maintenance of the population. After all, we compare the results obtained through numerical simulation with collected data from traps, as an attempt to validate the forecasting model of population dynamics and to estimate the adult female abundance. Through the modeling, we expect to show the importance to collect monthly real data from urban endemic regions in order to encourage and support surveillance schemes continuously

## Genetic Instability, Neutral Evolution, and Dynamic Precision Medicine of Cancer

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Cancer development is an evolutionary process, driven by mutation and selection. Loeb's "mutator hypothesis" postulates that enhanced genetic instability is required to evolve cancers. This talk will clarify a 40 year controversy concerning the truth of the mutator hypothesis, by introducing the concept of cancer development efficiency, and by applying theoretical methods designed for sparse experimental data. Cancer evolution has similarities with species evolution but also important differences. I will outline some of these differences, including results from the deepest most accurate sequencing of a solid tumor done to date. Finally, cancer treatment has also evolved, from an empirical science of killing dividing cells, to the current era of "precision medicine", exquisitely targeted to molecular features of individual cancers. However, current precision medicine views a single individual's cancer as largely uniform and static. Moreover, from a strategic perspective, it thinks primarily of the current therapeutic maneuver. In contrast, dynamic precision medicine plans further ahead, explicitly considers intratumoral heterogeneity and evolutionary dynamics, and may lead to the next level of therapeutic benefit beyond current personalized medicine.

## Waning immunity, distributed delays, multiple serotypes and reinfection

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Vector-borne diseases are a growing Public Health concern, to the extent that mosquitoes in particular have been labelled the most lethal animal for Humans. After an historical overview of the mathematical modeling of mosquito-borne diseases, with an emphasis on malaria and Dengue virus, we will present the difficulties inherent in modeling diseases with multiple serotypes and the incorporation of time delays to represent waning immunity.

## Agent-Based and Continuous Models of Locust Hopper Bands

Andrew J. Bernoff (speaker)<sup>a</sup>, Michael Culshaw-Maurer<sup>b</sup>, Maria D'Orsogna<sup>c</sup>, Sarah DeVore<sup>d</sup>, Leah Edelstein-Keshet<sup>e</sup>, Rebecca Everett<sup>f</sup>, Maryann Hohn<sup>g</sup>, Ryan Jones<sup>h</sup>, Stephen Schein<sup>i</sup>, Christopher Strickland<sup>j</sup>, Chad M. Topaz<sup>k</sup>, Jasper Weinburd<sup>l</sup>, and Jialun Zhang<sup>m</sup>

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Locust swarms pose a major threat to agriculture, notably in northern Africa, the Middle East and Australia. In the early stages of aggregation, locusts form hopper bands. These are coordinated groups that march in columnar structures that are often kilometers long and may contain millions of individuals. We report on two models for the formation of locust hopper bands. The first is a two-dimensional agent-based model (ABM) that incorporates intermittent motion, alignment with neighbors, and social attraction/repulsion, all behaviors that have been validated in experiments. Using a particle-in-cell computational method, we simulate swarms of up to a million individuals, which is several orders of magnitude larger than what has previously appeared in the locust modeling literature. We observe hopper bands in this model forming as an instability. Our model also allows homogenization to yield a system of partial integro-differential evolution equations. We identify a bifurcation from a uniform marching state to columnar structures, suggestive of the formation of hopper bands. The second is a one-dimensional ABM that introduces a resource (food) and includes foraging. Here homogenization yields a hyperbolic system of PDEs. Both the ABM and the PDEs manifest pulse solutions which are reflective of field observations. We reflect on the fact that both these models allow reductions that can be analyzed via methods from the study of dynamical systems.

## Using Glucose to Test a Rhythmogenic Mechanism in Pancreatic $\beta$ -Cells

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The secretion of insulin from the pancreas is pulsatile, with period of roughly 5 min, due to the periodic bursting electrical activity of the hormone-secreting  $\beta$ -cells that form clusters called islets of Langerhans. For several decades, there has been speculation about the type(s) of ion channel that drives the bursting. That is, the channel type that initiates and terminates each burst active phase in a periodic fashion. A leading contender is the ATP-sensitive K<sup>+</sup> channel (K(ATP) channel) that is inactivated by elevations in the ratio of ATP to ADP in the cell. This ratio has been shown to oscillate in phase with the bursting electrical activity, so it is natural to postulate that these nucleotide oscillations cause oscillations in K(ATP) ionic current, which drives the bursting. Testing this hypothesis, however, is quite difficult. Pharmacological or genetic manipulations that upregulate or downregulate the channel activity terminate bursting, but the same could be said with manipulation of any of the other ionic currents. What is needed is a non-invasive approach that establishes causation and not simply correlation. In this presentation, we discuss such an approach. In particular, we demonstrate that if activity-dependent oscillations in the K(ATP) current drive bursting, then changes in the level of glucose (which is metabolized to form ATP from ADP) will have little effect on the peak, nadir, or average of the oscillations in ATP/ADP. If some other current drives bursting, then an increase in glucose concentration will result in an increase in all three features of the nucleotide ratio. We use fast/slow analysis to establish this result, and demonstrate its generality using a variety of models for  $\beta$ -cell bursting.

## Serotonin circuitry in the brain

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In order to understand depression and other neuropathies, we have been collaborating with an electrochemist who measures dynamical changes in serotonin in the extracellular space in the brain. To interpret her data, we have used a mathematical model of serotonin synthesis, release and reuptake that we published in 2010 and various updated versions of the model. In 2014, we used an updated version of our serotonin model to investigate recordings made in the substantia nigra. Mathematical modeling was used to show that there are two distinct reuptake mechanisms for serotonin. The model also showed that autoreceptor effects are long-lasting, on the order of 30 seconds to a minute. In recent work, we use partial differential equations models to show that complicated reuptake curves with double humps occur because of the diffusion of released serotonin from one region to another. Current work involves the effect of neuroinflammation and histamine on serotonin release.

# Modelling dose dependent immune responses in acute Zika infection

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The key mechanisms of immune control of acute Zika virus infection are not fully understood, and furthering our knowledge of the within host dynamics of Zika virus will be important to the development of effective antiviral strategies. The majority of within host dynamics research has been performed in non-human primate (NHP) models of Zika infection, and understanding the role of inoculum dose is an important component in being able to translate results from a controlled experimental infection to a natural infection. Here we use mathematical modelling to analyze the within host dynamics of Zika virus in NHPs after infection at different inoculum doses. We find strong evidence for innate immune control of plasma viral load and dose dependence in the timing or strength of this immune response.

## Optimizing docetaxel scheduling to delay progression in metastatic prostate cancer patients receiving hormone therapy

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Continuous androgen deprivation therapy (ADT) has been the standard of care for patients with metastatic, hormone sensitive prostate cancer since the 1940s. Treating concurrently with docetaxel (DOC) chemotherapy has been shown to significantly improve median overall survival from 47.2 months with ADT alone to 57.6 months with concurrent treatment ( $p=0.0018$ ) (PMID: 29384722). We developed a mathematical model of prostate cancer stem and non-stem cell dynamics, and serum prostate specific antigen levels during concurrent treatment with ADT and DOC. We generate highly accurate fits to the longitudinal data of 100 patients receiving ADT treatment with docetaxel either given at the initiation of ADT treatment (castration nave, 59 patients, up to 6 cycles) or after the development of castration resistant prostate cancer (castration resistant, 41 patients, up to 10 cycles) ( $R^2 = 0.79$ ). As androgen-independent prostate cancer stem cells are sensitive to docetaxel, simulations show that early administration of chemotherapy results in sufficient reduction of the prostate cancer stem cell population. In contrast, late administration is unable to efficiently combat the large stem cell population that has developed during androgen deprivation, thereby resulting in shorter time to resistance. Model simulations show that the stem cell self-renewal rate is prognostic for development of resistance post DOC administration. We also use model simulations to show that castration nave patients may receive significant increase in time to progression if treated intermittently with DOC, when compared to concurrent ADT and DOC.

## Voltage-sensor domains modulate Nav1.5 inactivation via domain IV coupling

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Voltage-gated sodium (Nav) channels mediate the upstroke of the action potential across excitable tissues. In contrast to the four-way symmetry of tetrameric voltage-gated potassium channels, Nav channels are single polypeptide chains with four non-identical domains. The prevailing theory is that domains I through III are tied to channel activation, whereas the delayed response of domain IV exclusively leads to inactivation. In this study, we investigate the role of each domain in a Nav channel isoform, Nav1.5, using both biophysical and computational approaches. The Bowie Lab has shown that mutating each domain such that it is fixed in the on position alters the voltage-dependence of channel inactivation in all four cases, but to different degrees. In contrast, only mutations in domain I and IV lead to changes in the voltage-dependence of channel activation. Similar experiments from another group have shown that, in Nav1.4, only domain IV mutations affect channel inactivation. To put these results in context with prior knowledge of Nav channel gating, we revised an existing Markov model for Nav1.4 to explain the complex effects of domain mutations in Nav1.5. Our numerical simulations suggest that domains I through III affect inactivation through varying degrees of coupling with domain IV, while domain I affects activation by being the rate-limiting step for pore opening. Furthermore, we find that different kinetic rates in Nav1.4 and Nav1.5 can explain the differential impact of charge neutralization on channel inactivation. This study provides a more complete understanding of the structural mechanisms that underlie Nav channel signalling and highlights the individuality of different Nav channel proteins.

# Multi-strain immuno-epidemiological model of dengue structured by dynamic host antibody level

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Infection by distinct Dengue virus serotypes and host immunity are intricately linked. In particular, certain levels of cross-reactive antibodies in the host may actually enhance infection severity. The coupled immunological and epidemiological dynamics of Dengue calls for a multi-scale modeling approach. In this work, we formulate a within-host model which mechanistically recapitulates characteristics of antibody dependent enhancement (ADE) in Dengue infection. The within-host scale is then linked to epidemiological spread by a vector-host partial differential equation model structured by host antibody level. The coupling allows for dynamic population wide antibody levels to be tracked through primary and secondary infections by distinct Dengue strains, along with waning of cross-protective immunity after primary infection. Analysis of both the within-host and between-host systems are conducted. Stability results in the epidemic model are formulated via basic and invasion reproduction numbers as a function of immunological variables. Additionally, we develop numerical methods in order to simulate the multi-scale model and assess the influence of ADE on disease spread and burden in the population.

## Heat-induced radiosensitization simulated in 3D tumour spheroids

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Modern cancer therapy often combines multiple treatment modalities to maximize treatment efficacy, while minimizing the risk of treatment related side effects. For dose prescription, and scheduling of these multimodality therapies, understanding and quantification of the biological effects induced is key. A systems oncology simulation framework for modelling combination treatments of radiation and hyperthermia (temperatures above physiological levels) in multi-cellular tumour spheroids is presented. The implementation of a hybrid cellular automaton model [1] was extended to simulate tumour spheroids, including the modelling of 3D geometries, oxygen diffusion, and treatment specific cell death mechanisms and cell clearance. Whereas radiation-induced cell death was modelled as proliferation dependent process mimicking mitotic catastrophe, heat-induced cell killing was independent of the cell proliferation status and implemented as a fast process, allowing for re-oxygenation of deeper cell layers. A high performance implementation of the model allowed simulation of large cell populations ( $10^5$  –  $10^7$  cells) that could be compared directly with experimental data obtained for spheroids formed from HCT116 cells (human colorectal carcinoma). Single modality and combination treatments for doses up to 10 Gy and/or 240 CEM43 were evaluated. Spheroid growth was monitored using time-lapse imaging on an Incucyte S3 imaging platform (Sartorius, USA) to visualize dynamic changes in spheroid diameter (contour segmentation) and distribution of dead cells (propidium iodide staining, fluorescent imaging). The simulation could successfully reproduce experimentally measured spheroid growth curves (coefficients of determination > 0.85 in all cases), and the extent to the central necrotic core (qualitative comparison only). The proposed framework provides an important step towards clinical modelling of combination treatments of radiation and hyperthermia. It allows for optimization of treatment combinations in terms of thermal and radiation doses delivered, as well as scheduling of these treatments under physiological microenvironmental conditions.

[1] Brüningk et al., J R Soc Interface, 2018

## Understanding the drivers of Epstein-Barr virus shedding with HIV-1 coinfection

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Epstein-Barr virus (EBV) infection is transmitted by saliva and is a major cause of cancer in people living with HIV/AIDS as well as in the general population. To better understand the determinants of oral EBV shedding we evaluated the frequency and quantity of detectable EBV in the saliva in a prospective cohort study of 85 adults in Uganda, half of whom were co-infected with HIV-1. Participants were not receiving antiviral medications, and those with HIV-1 co-infection had a CD4+ T cell count >200 cells/mm<sup>3</sup>. Daily, self-collected oral swabs were collected over a 4-week period. Compared with HIV-1 uninfected participants, co-infected participants had an increased frequency of oral EBV shedding (IRR=1.27, 95% CI=1.10-1.47). To explain why EBV oral shedding is greater in HIV-1 co-infected participants, we developed a stochastic, mechanistic mathematical model that describes the dynamics of EBV, infected cells, and antiviral cellular immune responses within the tonsillar epithelium, and examined parameter-specific differences between individuals of different HIV-1 infection statuses. We fit the model to our observational data using Approximate Bayesian Computation. After fitting, model simulations showed high fidelity to daily oral shedding time-courses and matched key summary statistics. Examination of the model revealed that higher EBV loads in saliva are driven by B cell activation causing EBV lytic replication in the tonsils, in combination with a less effective EBV-specific cellular immune response. Thus, both these factors contribute to higher and more frequent EBV shedding in HIV-1 co-infected individuals compared to HIV-1 uninfected individuals. These conclusions were further validated by modelling daily oral EBV shedding in a 26-participant North American cohort. Our results provide insights into the determinants of EBV shedding and implicate B cell activation to be a potential therapeutic target to reduce EBV replication in HIV-1 co-infected individuals at high risk for EBV-related malignancies.

## Slowly varying modulation of neural networks

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The neurotransmitter acetylcholine has been shown to modulate the firing properties of several types of neurons through the down-regulation of voltage dependent potassium currents such as the muscarine-sensitive M-current. In particular, experimental work has shown that this current can switch the phase resetting curves from type I to type II and computational models have studied the resulting change in the synchronization of networks of such neurons. In the brain, levels of acetylcholine change with activity. For example, acetylcholine is higher during waking and REM sleep and low during slow wave sleep. Thus an accurate model of the effects of acetylcholine should include slow variation of this neurotransmitter.

Using a phase model reduction we study the effect of a slowly varying M-current on the synchronization properties of a model for cortical pyramidal cells. We show that as the current is downregulated or upregulated the phase model passes through two pitchfork bifurcations, which are associated in the full model with the transition between synchronous and asynchronous behaviour. The criticality of the pitchfork bifurcations depends on the neural model and whether the coupling is inhibitory or excitatory. We show that periodic slow passage through these pitchfork bifurcation leads to a hysteresis loop and study how different properties of the model affect this loop and the transitions between synchronous and asynchronous behaviour. Numerical simulations confirm the results of the phase model analysis.

## Evolutionary stability of ideal free dispersal under spatial heterogeneity and time periodicity

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Roughly speaking, a population is said to have an ideal free distribution on a spatial region if all of its members can and do locate themselves in a way that optimizes their fitness, allowing for the effects of crowding. Dispersal strategies that can lead to ideal free distributions of populations using them have been shown to exist and to be evolutionarily stable in a number of modeling contexts in the case of habitats that vary in space but not in time. Those modeling contexts include reaction-diffusion-advection models and analogous models using discrete diffusion or non-local dispersal described by integro-differential equations. Furthermore, in the case of reaction-diffusion-advection models and their non-local analogues, these are strategies that allow populations to achieve an ideal free distribution by using only local information about environmental quality and/or gradients. We show that in the context of reaction-diffusion-advection models for time periodic environments with spatially varying resource levels, where the total level of resources in an environment fixed but its location varies seasonally, there are strategies that allow populations to achieve an ideal free distribution. We also show that those strategies are evolutionarily stable. However, achieving an ideal free distribution in a time periodic environment requires the use of non-local information about the environment such as might be derived from experience and memory, social learning, or genetic programming.

## Biofilm spread on surfaces

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Recent experiments of *Bacillus subtilis* biofilm spread on surfaces suggest that their structure is defined by the interplay of elastic deformations and liquid transport within the biofilm, in response to the cellular activity and the interaction with the surrounding environment. We propose a poroelastic model for biofilm spread on agar surfaces. The motion of the boundaries can be described by the combined use of Von Kármán type approximations for the agar/biofilm interface and thin film approximations for the biofilm/air interface. Bacterial activity informs the macroscopic continuous model through source terms and residual stresses, either phenomenological or derived from microscopic models. Numerical simulations show that the model captures observed qualitative behavior such as accelerated spread and wrinkle formation.

# Innate Immune System Regulation in Health and Disease

Tyler Cassidy

Immune response to acute infection must strike a delicate balance of maximizing pathogen clearance while minimizing tissue damage. The chemical messengers responsible for this balance are pro- and anti- inflammatory cytokines. Pro-inflammatory cytokines drive the immune recruitment necessary for pathogen destruction while anti-inflammatory cytokines ensure that the acute immune response terminates. The production of pro- and anti- inflammatory cytokines is tightly regulated to ensure efficient immune response to challenge. However, dysregulation of cytokine production can lead to chronic inflammatory disease, like rheumatoid arthritis, or insufficient immune response to infections. We develop a mathematical model of monocyte and neutrophil production to study the immunohematopoietic regulation of white blood cell production. We use this model to understand cytokine regulation of cell production in health, during dynamical diseases, and in response to infection.

## Predicting cytotoxicity of natural killer cell

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Natural killer (NK) cells are lymphocytes that are capable of lysing their target cells. Target cells are recognized when their ligands bind to receptors expressed by NK cells, resulting in the stimulation of NK cells. Previous studies reported numerous tumor ligands and NK cell receptors with their roles, to stimulate or to inhibit target cell lysis. However, they are limited to qualitative roles without considering quantitative relation between receptor-ligand binding and cytolysis. In this study, the quantitative role of receptor-ligand binding was investigated. We built a mathematical model which can explain the relation between receptor-ligand binding and cytotoxicity. The model successfully predicted cell lysis of leukemia cell lines.

## A Dynamical Model to Forecast Seasonal Influenza

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Decades of research using mathematical and statistical models of infectious disease spread at the population level have greatly improved scientific understanding of the dynamics of epidemics. In particular, in past high-profile outbreaks (e.g., 2001 foot-and-mouth disease, 2003 SARS, 2009 H1N1, 2010 Cholera, 2014 Ebola, 2016 Zika), “real-time” epidemic outbreak forecasting generated interest because it can provide quantitative tools to support time-critical decisions. But, there is still no widespread agreement among scientists on the best modelling approaches to forecast a given epidemic.

Here, I will present a modelling framework that is particularly well adapted – yet rarely used – to forecast seasonal epidemics of respiratory infections (e.g., influenza, respiratory syncytial virus). This framework draws from recent theoretical advances in mathematical epidemiology and Bayesian statistics. The disease transmission process is described by a renewal equation, where the generation interval distribution (the time interval between infection and a secondary case) plays a fundamental role. Forecast uncertainty is propagated by incorporating a hierarchical statistical model. I will also present a practical application to forecast seasonal influenza in Canada.

## Optimizing Ligand Properties in Pancreatic Cancer Targeted Therapy

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Targeted therapies show promise for being more specific and less toxic. However, in order to be successful, the drugs must reach all tumor cells in sufficient quantities. We combined modern optimization techniques and agent-based computational modeling to determine the properties of targeting ligands that lead to optimal cellular uptake within the heterogeneous tumor tissue. We will illustrate this approach using experimental data on pancreatic tumors that overexpress the toll-like receptors 2 (TLR2) and a specific fluorescent TLR2 ligand. Using a 2D model of the pancreatic cancer tissue, we aimed at manipulating ligand properties to overcome tissue spatial barriers benefiting from the dynamic TLR2 recycling. Specifically, we used rigorous mathematical optimization to obtain optimal ligand diffusion coefficients and ligand-receptor binding affinities when the following two objectives were considered: maximizing distribution of drug molecules among cells, and minimizing the escape of drugs from the tumor tissue without cellular uptake. Theoretically, the optimal ligands are those that bind to cell receptors with 100% probability, a value which may not characterize most drugs. Therefore, we formulated multiple optimization problems considering different types of drugs to find TLR2 recycling times that allows for the maximum benefit from the targeting ligands. This analysis may prove useful in the selection of drugs based on tumor-specific or even patient-specific TLR2 recycling dynamics, supporting personalized pancreatic cancer treatments.

*Title:* Integrating QSP Modeling In Phase I Clinical Drug Development of Mosunetuzumab in Relapsed/Refractory Non-Hodgkin's Lymphoma

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*Abstract:*

T cell-engaging bispecific antibodies (T-BsAb) are becoming important molecular entities in the development of immune-oncology agents. The promises in clinical efficacy with the potent mechanism of action comes with the potential acute toxicity concerns, driven by the systemic cytokine release following T cell activation. A key strategic component of the Phase I clinical development of mosunetuzumab, an anti-CD20/CD3 T-BsAb, is to maximize the therapeutic window of treatment in relapsed/refractory non-Hodgkin's Lymphoma (r/r NHL) patients. A QSP model was built based on in-house preclinical and clinical data from literature to characterize the pharmacological drivers for safety and efficacy. Model-based simulations were used to evaluate the systemic cytokine profiles following various clinical dosing regimens of mosunetuzumab, and used as the basis for the design of Phase I dose finding protocol. The presentation will discuss strategies to integrate modeling in decision making in an impactful manner and in the dynamic context of Phase I drug development in oncology.

## Modeling novel strategies to block malaria transmission

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Transmission of the deadly parasite *Plasmodium falciparum* between humans requires a bite by an infectious *Anopheles* mosquito. As a result, these bites result in hundreds of thousands of deaths each year. Mass distribution of insecticide-treated bed nets have vastly reduced the burden of malaria in recent years, but widespread insecticide resistance in *Anopheles* populations has begun to be observed. Novel tools that differ from fast-acting insecticides are needed to combat malaria transmission and avoid a resurgence in malaria related deaths. Here, we use recent evidence on compounds that directly target the parasite in the mosquito in a discrete-time model of *Anopheles* mosquito population dynamics and malaria transmission. Incorporating these types of effects into our model predicts that the inclusion of these compounds on mosquito nets would significantly reduce the burden of malaria across all ranges of prevalence and levels of insecticide resistance. These compounds show great promise in preventing transmission of the malaria parasite without completely abrogating the *Anopheles* mosquito population.

## Bayesian method for Modeling household transmission dynamics

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We describe a method for analyzing the within-household network dynamics of a disease transmission. We apply it to analyze the occurrences of endemic diarrheal disease in Cameroon, Central Africa based on observational, cross-sectional data available from household health surveys. To analyze the data, we apply formalism of the dynamic SID (susceptible-infected-diseased) process that describes the disease steady-state while adjusting for the household age-structure and environment contamination, such as water contamination. The SID transmission rates are estimated via MCMC method with the help of the so-called synthetic likelihood approach. The SID model is fitted to a dataset on diarrhea occurrence from 63 households in Cameroon. We show that the model allows for quantification of the effects of drinking water contamination on both transmission and recovery rates for household diarrheal disease occurrence as well as for estimation of the rate of silent (unobserved) infections.

## Asymptotic Approximation for Biofilm Growth Models

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Experiments involving bacterial biofilms consist of growing colonies within flow cell chambers. The size of the flow cell chambers can vary, but what is common among these experiments is that (a) the region where observations are made is a small fraction of the chamber, (b) observations can be obscured when close to the fluid inlet, outlet, or sidewalls. For mathematical models of biofilms to be properly compared to experimental observations, information about the local environment surrounding the observation location is needed. However, computing a biofilm model over a full flow cell is prohibitively expensive, while experimental measurements of environmental factors are only measurable at the inlet and outlet. Thus, there is a need to develop a model that can estimate the local environment in a flow cell. We present in this talk an asymptotic approximation method for computing the oxygen concentrations in a whole flow cell. The method effectively reduces the dimensionality of the problem by one and thus making the solution computationally tractable.

# Immigration-induced transition in a regulated multispecies birth-death-immigration process

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Power-law-distributed species counts or clone counts arise in many biological settings such as multispecies cell populations, population genetics, and ecology. This empirical observation that the number of species  $c_k$  represented by  $k$  individuals scales as negative powers of  $k$  is also supported by a series of theoretical birth-death-immigration (BDI) models that consistently predict many low-population species, a few intermediate-population species, and very high-population species. However, we show how a simple global population-dependent regulation in a neutral BDI model destroys the power law distributions. Simulation of the regulated BDI model shows a high probability of observing a high-population species that dominates the total population. Further analysis reveals that the origin of this breakdown is associated with the failure of a mean-field approximation for the expected species abundance distribution. We find an accurate estimate for the expected distribution  $\langle c_k \rangle$  by mapping the problem to a lower-dimensional Moran process, allowing us to also straightforwardly calculate the covariances  $\langle c_k c_\ell \rangle$ . Finally, we exploit the concepts associated with energy landscapes to explain the failure of the mean-field assumption by identifying a phase transition in the quasi-steady-state species counts triggered by a decreasing immigration rate.

## STOCHASTIC MODELING OF INTRACELLULAR TRANSPORT IN NEURONS

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We present a mathematical framework to analyze the intracellular transport inside a neuron. We study the transport on a parallel arrangement of microtubules inside the axon (axonal transport), as well as various tangled networks of microtubules inside the soma (somatic transport). For the former, our model captures the spatial dynamics and interactions of a motor and cargo particles, and the mean attachment time of the motor to a microtubule is computed. For the latter, we analyze the effects on the transport of particle switching at the microtubule intersections. In all cases, we have obtained the effective velocity and diffusion coefficient for the transport at the cellular scale.

## Microtubule cytoskeleton self-organisation is robust in *Drosophila* epithelium

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The microtubule cytoskeleton is a self-organising dynamic network along which cellular components are transported to their biologically relevant locations. In particular the transmembrane protein E-cadherin, is crucial in maintaining cell-cell adhesion in tissue. Throughout *Drosophila* embryo development the cytoskeleton self-organises primarily governed by cell geometry [1].

Using stochastic simulations, genetic manipulations of the *Drosophila* epithelial cells and a probabilistic toy model we show that cytoskeleton self-organisation depends on cell geometry and microtubule seed density alone. Thus the self-organisation of microtubules; the network for intracellular transport, is robust.

[1] Gomez, Chumakova, Bulgakova, Brown, *Nature communications* 7 (2016): 13172.

# A renewal reward approach for studying models of intracellular transport

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Many biological agents transition between different biophysical states during movement. For example, proteins inside cells bind and unbind to and from cellular roads called microtubules, switching between bidirectional transport, diffusion, and stationary states. Since models of intracellular transport can be analytically intractable, asymptotic methods are useful in investigating the effective cargo transport properties as well as their dependence on model parameters. We consider these models in the framework of renewal processes and derive the effective velocity and diffusivity of cargo at large time for a general class of problems. We illustrate applications of the proposed method to macroscopic models of protein localization and microscopic models of processive cargo movement by teams of molecular motor proteins.

## Early events during hepatitis B virus infection

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Experimental studies in non-human primates inoculated with hepatitis B virus have shown that virus dose influences the kinetics of virus spread and the disease outcome. In particular, high and low doses lead to 100% liver infection, while intermediate doses lead to less than 0.1% liver infection. To determine the relationship between virus dynamics, percentage of liver infection, and immune priming we developed an in-host mathematical model that considers the effects of cellular immune responses in controlling the disease. We fitted the model to data and predicted correlations between dose size, the timing of the immune response, the potency of immune effects, and disease outcome. Such results can guide our understanding of the virus-host dynamics that control the virus or permit a transition to chronic disease.

## Lying in wait: Controlling bacterial infections using latent phage-antibiotic synergy

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The canonical bacteriophage is obligately lytic: the virus infects a bacterium and hijacks cell functions to produce large numbers of new viruses which burst from the cell. These phages are well-studied, but there exist a wide range of coexisting phage lifestyles that are less understood. Temperate phages exhibit both a lytic cycle and a latent (lysogenic) cycle, in which viral genomes are stored within the bacterial host. Meanwhile, chronic phages hijack cell functions to produce more phage without killing the cell; chronic phages may also exhibit a latent stage in addition to the productive stage. Here, we investigate the ecology of these competing phage strategies. We demonstrate the environmental and evolutionary conditions under which each strategy is dominant. Understanding these conditions aids in control of human bacterial infections using phage; because antibiotics are capable of inducing latent phage, antibiotics and latent phage act synergistically to control bacterial infections.

## Homogenisation techniques for populations dynamics on strongly heterogeneous landscapes

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One important challenge in spatial ecology is to determine how local environmental variation and corresponding animal movement behaviours drive the large scale patterns of population abundance that we observe. Many organisms, in particular insects such as butterflies, respond to habitat edges and express preference for particular habitat types. While it is known that such preferences can affect important quantities such as invasion speeds, we do not have general tools to ask how preference can affect other aspects of landscape level patterns of population abundance. In this talk we present a novel homogenisation technique to allow us to approximate the large scale dynamics of a system driven by local reaction-diffusion processes coupled with behavioural responses to habitat edges. We illustrate our approach with an example of logistic growth and show how local scale dynamics can scale up to the landscape scale in non-intuitive ways.

## Robust estimation of factor loadings with application to postpartum depression

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Factor analysis is a technique for understanding how symptoms covary. In psychiatry, estimated factors are used to explain variation in large imaging datasets rather than using traditional diagnoses. However, estimation of factor structure is notoriously sensitive to factor dimension and characteristics of the data. We will introduce an estimation technique that aims to address these issues and compare this technique to standard estimation in simulation. As a case study, we explore the factor structure of psychiatric symptoms in the postpartum period. Our long-term goal is to gain understanding of how individuals might experience and report postpartum depression differently.

# Nested Active Learning for Efficient Model Contextualization and Parameterization

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**Introduction:** Sepsis is an inflammatory condition with a mortality rate of between 28%-50%. Numerous mechanistic computational simulations of acute inflammation and sepsis have been utilized over the past two decades. These models have demonstrated that the sepsis population is much more heterogeneous than previously thought and this can be reflected by utilizing a range of multidimensional parameters that correlate to biologically plausible behaviors and phenotypes. Despite insights generated from these methods, there remain considerable challenges in the calibration and parameterization of the models. The description of the environment in which a biomedical simulation operates (model context) and parameterization of internal model rules (model content) requires the optimization of a large number of free-parameters; given the wide range of variable combinations, along with the intractability of *ab initio* modeling techniques which could be used to constrain these combinations, an astronomical number of simulations would be required to achieve this goal. In this work, we utilize a nested active-learning workflow to efficiently parameterize and contextualize an agent-based model of sepsis. **Methods:** Billions of microbial sepsis patients were simulated using a previously validated agent-based model (ABM) of sepsis, the Innate Immune Response Agent-Based Model (IIRABM). Contextual parameter space was examined using the following parameters: cardio-respiratory-metabolic resilience; two properties of microbial virulence, invasiveness and toxigenesis; and degree of contamination from the environment. The models internal parameterization, which represents gene expression and associated cellular behaviors, was explored through the augmentation or inhibition of signaling pathways for 12 signaling mediators associated with inflammation and wound healing. We have implemented a nested active learning approach in which the clinically relevant model environment space for a given internal model parameterization is mapped using either a small Artificial Neural Network (ANN). The outer AL level workflow is a larger ANN which uses active learning to efficiently regress the model coefficients for the lower level, as a function of the models internal parameterization. **Results:** A brute-force exploration of the IIRABMs content and context would require approximately  $3 \cdot 10^{12}$  simulations, and the end result would be a coarse representation of a continuous space. We have reduced the number of simulations required to efficiently map the clinically relevant parameter space of this model by approximately 98%. Additionally, we have shown that more complex models with a larger number of variables may expect further improvements in efficiency.

## Remote Sensing, Weather, and Demographic Data for Mosquito-Borne Disease Risk

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\*Presenter

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Mosquito-borne diseases such as Zika, dengue, and chikungunya viruses have dynamics coupled to weather, ecology, human infrastructure, socio-economic demographics, and behavior. We use time-varying remote sensing and weather data, to predict risk through time for dengue outbreaks in Brazil using statistical methods. Our statistical model indicates that the relationships between the variables are complex, but that quantifying risk is possible with the right data at appropriate spatio-temporal scales. We show that important ecological variables and disease risk vary with geography across the country. Ecological drivers exhibit low and high frequency behavior that change risk locally with lags in time.

## Interpreting super-resolution microscopic imaging of B cell surface receptors

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In common with many cell-surface receptors, the spatial organization of B cell receptors is expected to strongly influence their signaling behaviour. In order to assess spatial organization at the scale of a few nanometers, we performed super-resolution imaging experiments on fixed cells using the dSTORM technique. We developed a novel graph-based algorithm to detect and quantify the clustering of fluorescent object blinks (StormGraph). We also developed a new approach to assess the degree of multiple counting of single labels, based on simple temporal and spatial models of the experimental system. I will describe the biological system and experimental methods, outline the construction and validation of our new algorithms, and then present results on B cell receptor organization at the nanoscale.

# Modeling insights into the collective cell polarization of heart progenitor cells

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During embryonic development, cells often migrate in groups. The heart progenitors of the ascidian Ciona provide one of the simplest examples of collective migration whereby just two cells migrate with defined leader-trailer polarity. The cells are also capable of migrating individually, albeit with imperfect persistence and with altered morphology. Thus, it appears that the polarization needed for directed migration is established in two cells better than in an individual cell. To understand the origin of this enhanced polarization in a collective, we develop a computational model to study the interplay between actomyosin contractility, cell-matrix adhesion, and biochemical feedback of molecular components. Three competing hypotheses are tested to understand the origin of the polarization: (1) mechanically, (2) biochemically, and (3) a combined mechanochemical pathway. Computational investigation of the emergent polarity in these three models and scans of the models' parameter spaces lead to insights into these different polarization mechanism.

## Building agent-based models of non-muscle myosin II filaments

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Non-muscle myosin II (NMMII) is a molecular motor that assembles into bipolar ensembles. NMMII ensembles bind, slide, and crosslink multiple actin filaments (F-actin) through motoring and crosslinking activity. Together, NMMII and F-actin form networks that generate contractile forces that drive many non-muscle cellular contexts, including cytokinesis. While the biophysics of NMMII individual motor domains is well-characterized, it is unknown how the motors in NMMII ensembles affect each others activities, and how the number of NMMII subunits affects network dynamics. Direct//Biophysical measurements of ensembles are difficult, but modeling of actomyosin networks has aided in discovering the complex behaviors of NMMII ensembles. To date, myosin ensembles have been modeled via several strategies, and while most result in global contractile behaviors, it remains unclear which strategies most accurately depict cellular activity. Previously, myosin clusters have been modeled as collections of fully discrete motors, or coarse-grained single entities representing clusters of motors, both with variable unbinding dynamics estimations: catch-, slip- and catch-slip bonding. Here, we used agent-based modeling, via Cytosim, to model NMMII ensembles via several strategies. Comparison of strategies in simulations of translocation on immobilized actin revealed only catch-slip motors progressively translocated. Conversely, coarse-grained ensembles with all unbinding dynamics estimations resulted in translocation, though catch-bonding motors were the least progressive and appeared not to translocate. In simulations of actomyosin rings, all motor types drove complete constriction of the ring, though again only catch-slip motors generated effective contractile forces when fully discretized. Comparison of actomyosin network structure during constriction between effective contractile simulation revealed aberrant fragmentation of rings with all but catch-slip-bonding NMMII ensembles. Together our data support the importance of discretely modeling all motor units on NMMII ensembles for accurately estimating connectivity and providing more efficient contractility of actin rings.

## Recent advances in understanding the dispersal of organisms: ideal and real

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The problem of understanding the ways organisms disperse, why they disperse the way they do, and what mechanisms they use to decide how to disperse has attracted considerable attention from both mathematical and empirical biologists. As a result, there have been significant recent advances in our knowledge of both what types of dispersal are optimal and how organisms actually disperse. In this talk, I will describe some results of both types and some current directions of research in the area. From the mathematical side, it has been established that in a system of competing populations that are otherwise ecologically identical except for their dispersal strategies, the populations that can best match their spatial distributions to those of their resources have an advantage. In particular, dispersal strategies that can produce an ideal free distribution (where the match is exact) have been shown to be evolutionarily steady and to be neighborhood invaders in various modeling contexts. In many models all members of each population are assumed to disperse in the same way, and dispersal is described in terms of a single matrix, integral kernel, or advection-diffusion operator. In a static environment with spatial variation, models suggest it is possible for a population to achieve an ideal free distribution on the basis of local information about the environment by choosing precisely the correct combination of advection and diffusion at each location. In the time-periodic case, it is still possible to achieve an ideal free distribution via advection and diffusion but it requires nonlocal information. On the empirical side, organisms seem to be able to find resources fairly well, but their dispersal patterns often involve switching between two or more modes of advection and/or diffusion rather than finely tuning a single mode. Specifically, many organisms seem to use large-scale random movement to search for resources then switch to small scale directed movement. In some situations organisms use nonlocal information in deciding how to disperse. The observed dispersal patterns again appear to be effective in allowing populations to match resources. There has been some work on modeling this type of dispersal with switching, but not too much. In this talk, I will describe some recent modeling work on understanding dispersal with nonlocal information use and/or switching between modes, and current projects aimed toward seeing how close theoretical populations can get to ideal resource matching by using dispersal strategies of the type observed in real populations. The talk is not based on any single paper but some of the work it will describe was done in collaboration with R.S. Cantrell, W.F. Fagan and members of his lab, Y. Lou, or X. Yu.

## Determining the Mechanisms of Combined Immunotherapy/Oncolytic Virotherapy Success for Treatment Personalization and Optimization through Computational Biology

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Immunotherapy is a modern anti-cancer strategy that relies on the activation of the immune system against cancer cells in a generalized or targeted way. In this vein, one method for immune-tumour targeting is oncolytic virotherapy that uses genetically modified viruses to preferentially attack and infect cancer cells, forcing them to undergo lysis and release tumour specific antigens that signal the immune system to mount an anti-tumour response. Theoretically, a combined approach to anti-cancer treatment leveraging immunotherapies like exogenous cytokine administration and oncolytic virotherapy would elicit an even greater immune response and improve patient outcomes, but ideal therapy regimens have yet to be determined. Using a computational biology approach, we modelled the interactions of susceptible and resistant tumour cell populations with oncolytic viruses and granulocyte-macrophage colony-stimulating factor (GM-CSF), a white blood cell growth factor, to determine the mechanisms regulating immuno-/oncolytic virotherapy in combination. Using an *in silico* clinical trial, we showed that improvements to long-term survival fractions in cohorts of patients with late-stage melanoma were achievable through an optimal, personalized regimen, suggesting promising avenues of investigation for combined GM-CSF and oncolytic virotherapy.

## Randomization for the susceptibility effect of infectious disease interventions

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Randomized trials of infectious disease interventions, such as vaccines, often focus on groups of connected or potentially interacting individuals. When the pathogen of interest is transmissible between study subjects, interference may occur: individual infection outcomes may depend on treatments received by others. Epidemiologists have used mathematical models of disease transmission to define the primary causal effect of interest – called the “susceptibility effect” – as a contrast in infection risk under treatment versus no treatment, while holding exposure to infectiousness constant. But this quantity can be difficult to estimate because exposure to infectiousness cannot always be measured precisely. A related quantity – the “direct effect” – is defined as an unconditional contrast between the infection risk under treatment versus no treatment. Mathematical epidemiologists have warned that failing to control for differential exposure to infection can confound estimates of the susceptibility effect, but the role of randomization in eliminating confounding remains unclear. In this paper, we show that under a widely recommended randomization design, the direct effect may fail to recover the sign of the true susceptibility effect of the intervention in a randomized trial when outcomes are contagious. Investigators who estimate the direct effect as an approximation to the susceptibility effect may wrongly conclude an intervention that protects treated individuals from infection is harmful, or that a harmful treatment is beneficial. The analytical approach uses a formal construction of infectious disease transmission to define the susceptibility effect. A novel probabilistic coupling argument reveals stochastic dominance relations between potential infection outcomes under different treatment allocations.

## Modeling visual circuit development of mice through synaptic plasticity

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The mammalian primary visual cortex contains a typical structure of connectivity between neurons, comprising circuits of synaptically-coupled cells that respond preferentially to similarly-oriented visual stimuli (e.g., horizontal bars). In the mouse, these orientation-preference neurons are scattered randomly throughout the cortex (called a “salt and pepper” orientation map), leading researchers to believe that the mouse visual cortex lacks organization. Experimentalists have shown, however, that cells sharing orientation preference are preferentially connected via a chemical synapse in adult mice. Further, cells that were derived from the same progenitor cell during development (called sister cells) are connected preferentially by an electrical connection called a gap junction during the first postnatal week, while chemical synapses are still being formed. Additionally, these sister cells tend to share an orientation preference and a chemical synapse in the adult mouse visual cortex. We construct a model of the mouse visual cortex during the first postnatal week and analyze the effect of gap-junctional coupling on the development of the synaptic connections. Through simulation of the model network, we show that cells containing gap junctions in the first postnatal week not only tend to share orientation preference in the developed cortex, but also these cells learn their synaptic connections faster than those that are not connected by a gap junction. We also propose that gap-junction coupling in the postnatal cortex can be a mechanism underlying the random salt and pepper orientation map that is typical of the adult mouse visual cortex.

## Population dynamics of monarch butterflies in highly fragmented landscapes

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Abundance of herbivorous insects is often assumed to be determined by the abundance of food resources. In the case of butterflies, these are usually larval host plants, i.e., food resources for growing caterpillars. One common assumption is that the larval host plants determine the carrying capacity. For example, past models of population dynamics of monarch butterflies have often implemented density dependent survival of caterpillars, and in some cases, assumed strict ratio dependence of the number of adult butterflies based on the number of available stems of their larval hostplants, milkweeds. An alternative assumption is that monarch butterfly population growth rates are limited by the time it takes adult butterflies to move through the landscape and encounter host plants. At landscape scales, milkweed cover for monarchs is about 0.01-1%, suggesting significant search-time limitation. In this talk, I use simple integrodifference equation models (parameterized with field and lab data for monarch butterflies) to explore population dynamics of monarch butterflies in these highly fragmented landscapes. I contrast the predictions of these models, which are based on time limitation, to past models of monarch butterfly population dynamics. For example, if host plants regulate populations in a density dependent manner, stopping habitat destruction will cause populations to stabilize. However, if search time for host plants affects population growth rate in a density independent manner, then populations will continue to decline, even if habitat destruction is stopped.

## A multifaceted approach to characterizing glioblastoma subpopulation dynamics

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Glioblastoma (GBM) is the most aggressive primary brain tumor and has a dismal median survival of only 15 months with current standard of care treatment. GBM is known to be spatially heterogeneous with multiple molecularly-distinct subpopulations, however the dynamic interactions and complete spatial layout of these subpopulations remains unknown. Current best practice analyzes GBM subpopulations through tissue biopsies, which are often not representative of the tumor as a whole. We aim to gain a spatiotemporal understanding of GBM subpopulations through a combination of patient images, image-localized biopsies, machine learning techniques and mechanistic modeling. Patient imaging paired with image-localized biopsies is used to train and validate a machine learning model that outputs spatial subpopulation maps. These spatial maps are then used as input to select appropriate reaction terms in a partial differential equation model, that is proposed to illuminate the mechanistic interactions between these subpopulations. The characterization of these subpopulation dynamics could be used to inform future personalized treatment regimes as well as to retrospectively reassess treatment response.

## Dynamic Features of Bistable Auditory Perception - A Modeling Perspective

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Past decades of auditory research have identified several acoustic features that influence perceptual organization of sound, in particular, the frequency of tones and the rate of presentation. One class of stimuli that have been intensively studied are sequences of tones that alternate in frequency. They are typically presented in patterns of repeating triplets  $ABA\_ABA\_\dots$  with tones  $A$  and  $B$  separated in frequency by several semitones ( $DF$ ) and followed by a gap of silence ‘\_’. Listeners hearing the sequence perceive either one auditory object (“stream integration”) or two separate auditory objects (“stream segregation”). The initial percept is typically integration while segregation builds up with a time course of seconds. The psychometric build-up function, BUF (from trial-averaging) is typically monotonic and depends on  $DF$ . However, accounting for the BUF transient phase requires understanding of how the initial percept is biased to integration. This talk introduces a novel dynamic neural-based model for bistable auditory perception. The model is structured as a 3-layer pseudo-mechanistic network based on evidence accumulation, not competition per se. It incorporates neuronal responses from the primary auditory cortex and describes the noisy evolution of evidence against the current percept. The model accounts quantitatively for key features of streaming behavior observed in human data collected by our lab. In particular, the model matches  $DF$ -dependent mean durations, gamma-like distributions for first and subsequent durations, as well as trends of BUFs. Acknowledgements: This work was done in collaboration with Anh P.Q. Nguyen (University of Iowa) and John Rinzel (New York University) and it was supported by NSF CRCNS 1515678.

## Evolution of Life History Strategies: Semelparity versus Iteroparous

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A classic question concerning life history strategies of biological populations and their ecological interactions involves reproductive timing and output and, specifically, the option between semelparity-annual (one reproductive event only in an individual's life, e.g. annual plants) and iteroparity-perennial (multiple reproductive events, e.g. perennial plants). Under what circumstances will evolution favor one of these strategies over the other? While early investigations suggested semelparity should be favored by evolution [1], subsequent studies have shown there is no simple answer to this question and that many factors can be in play, including density dependence, variable environmental conditions, and many others. Recent studies have further proposed, on the basis of an extensive review of the biological literature concerning the observed reproductive strategies of biological populations across many taxa, that reproductive parity should not be binary, but instead should be a continuous variable [3]. Darwinian dynamic (evolutionary game theoretic) modeling methodology involves continuous traits and is suitable for this approach.

In this talk I formulate Darwinian dynamic versions of some standard discrete time population models. The focus is on determining conditions under which population extinction states are stable and on the bifurcations that result upon destabilization. The mathematical analysis concerns dynamics (local and global) involving the multiple equilibrium attractor scenarios that arise and the life history strategies implied by the trait components of the equilibria. Results include conditions under which semelparous-like equilibria and iteroparous-like equilibria exist and are stable and also conditions under which they either are or are not ESS equilibria (i.e. are equilibria with evolutionarily stable strategies) [2]. A focus is on the role of density dependent reproduction and survival.

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## Control of plant cell growth through cortical microtubule mechanics

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In growing plant cells, parallel ordering of microtubules (MTs) along the inner surface of the cell wall/membrane influences the direction of cell expansion and thereby plant morphology. In stem and root cells, for correct expansion, MTs must bend in the high-curvature direction along the cylindrically shaped cell wall/membrane in order to form the required circumferential arrays. Previous studies, which have recapitulated the self-organization of these arrays, ignored MT mechanics and assumed MTs follow geodesics of the cell surface. Here, we show, through analysis of a derived Euler-Lagrange equation, that an elastic MT constrained to a cylindrical surface will deflect from high to low curvature directions to minimize bending energy as it grows but only at low anchor density. At high anchor density, MTs follow geodesics. This result justifies the previous self-organization results for arrays in growing stem and root cells at high anchor density but predicts incorrect array orientation at low anchor density in those cells. It also provides a mechanism by which plant cells, in general, can regulate array orientation and hence growth and is consistent with experiments on mutant plants that have modified MT anchoring dynamics and misoriented arrays.

## Modeling hepatitis B virus infection in primary human hepatocytes

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Chronic hepatitis B virus (HBV) infection is a serious global health problem, which causes advanced liver diseases, such as cirrhosis and hepatocellular carcinoma. Understanding of early HBV dynamics at the molecular level in primary human hepatocytes (PHHs) is lacking. I will provide in my talk a detailed characterization of intracellular and extracellular HBV kinetics during infection and anti-HBV treatment in PHHs along with our understanding of HBV-host dynamics via mathematical modeling.

## Enzootic Avian Malaria in Hawaiian Honeycreepers: modeling the effect of control

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Avian malaria is a mosquito-borne parasitic disease of birds that has been identified as a cause of the decline of Hawaiian forest birds, in particular the endemic Hawaiian honeycreepers. We formulate a compartmental model of the transmission dynamics of avian malaria between honeycreepers and mosquitoes as a system of ordinary differential equations. Reproduction numbers as well as criteria for the existence and stability of disease-free and enzootic equilibria are derived. The basic reproduction number exceeds one for all populations of apapane and low-elevation Hawaii amakihi, indicating that these populations are likely responsible for the maintenance of active avian malaria transmission in other honeycreeper populations. We consider the population and disease control impacts of larval mosquito source reduction and captive propagation, showing that the elimination of enzootic avian malaria is likely impossible through the application of these management strategies alone. However, the long-term densities of some honeycreeper populations may be returned to “healthy” levels through application of these strategies at appropriate intensities. Further work will determine the population impacts of management scenarios that incorporate modern forms of vector control such as sterile-insect techniques or Wolbachia-based methods.

# The IGP Model and Free Boundary Problems

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In this report, we first start from the Logistic model with fixed boundaries, analyze the limitations of solutions of initial boundary value problems in fixed regions, and propose the necessity of establishing corresponding free boundary problems. As examples, the modeling of free boundary problems with practical application background, such as population invasion, infectious diseases and information dissemination, is given. Finally, some recent studies on the dynamic properties of IGP models with free boundary and diffusion are introduced. We consider a diffusive intraguild predation model with intraspecific competition and free boundaries in one dimensional space. Our main objective is to portray the asymptotic behaviors of the IG predator species expanding via the free boundaries. In both cases, we prove a spreading-vanishing dichotomy for this model, specifically, the IG predator species either successfully spreads to the entire space as  $t \rightarrow \infty$  and survives in the new territory, or fails to establish and dies out in the long run. The long time behaviors of  $(R, N, P)$  and criteria for spreading and vanishing are also obtained. In addition, when spreading happens, we propose an upper bound and a lower bound for the asymptotic spreading speeds of the free boundaries.

## miRNA combinatorial regulation of networks driving EMT

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Cancer cells reactivate the gene expression programs of EMT and MET through a wide range of mechanisms, and better understanding of these regulatory processes will lead to the identification of therapeutically actionable targets. MicroRNAs (miRNAs) are important post-transcriptional regulators of gene expression, functioning in part by facilitating the degradation of target mRNA transcripts. MiRNAs have an established role in controlling EMT, and many studies have demonstrated the role of individual miRNAs using overexpression at levels greatly exceeding physiological abundance, which can in turn lead to off-target effects, and over-estimation of functional effects. Computationally, we place the TCGA breast cancer samples, and a collection of ~60 breast cancer cell lines on a landscape defining epithelial and mesenchymal molecular phenotypes, and use this as a tool to explore phenotypic transitions. Analysing a human mammary cell model of EMT with endogenous changes in miRNA expression, we identify a set of miRNAs, including the miR-200 and miR-182/183 family members, that cooperate in post-transcriptional regulation by targeting a network of interacting proteins and both reinforcing and buffering transcriptional output. We demonstrate that combinatorial treatment with these miRNAs could induce MET with miRNA concentrations much closer to endogenous levels and with less off-target effects. This discovery, that co-operative targeting by miRNAs is important for their physiological function, has opened the way for a more-nuanced understanding of post-transcriptional regulatory processes.

# Holes, rings and clusters: Characterizing large scale structures in filamentous networks

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Proteins such as actin polymerize into long filaments. These filaments can interact with a variety of proteins such as linkers or motor proteins, and these interactions can organize the filaments into large scale structures. Ring channels, circular openings in developing oocytes of the nematode worm *Caenorhabditis elegans*, are one such structure which are constructed by actin filaments. Previous work in our group identified opposing roles for the non-muscle myosin motor proteins NMY-1 and NMY-2 for the maintenance of these ring channels. To simulate the emergence of these structures, we have been using the stochastic simulation software MEDYAN, developed by the Papoian group at the University of Maryland, to investigate the emergence of large scale structures such as clusters and rings or holes as a result of actin and motor protein interactions. We have adapted topological measures including Betti numbers to characterize the spatial and temporal dynamics of these structures. Our current results suggest ring shaped structures rely on a balance of linker and motor proteins, and transitioning from a ring type hole to a more homogeneous actin meshwork can be accomplished by regulation of motor protein activity or abundance.

## Mathematical modeling reveals improved PARPi-radiation therapy administration schedules

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**Background:** Radiation therapy (RT), the use of ionizing radiation to induce DNA damage in cancer cells, is a commonly employed treatment modality in oncology. In an attempt to increase the effectiveness of RT, the use of radiation sensitizing drugs in combination with RT is currently being investigated. One such type of drug being evaluated in combination with RT in early phase clinical trials is PARP inhibitors (PARPi). PARPi sensitize cancer cells to RT by inhibiting DNA damage repair. However, it is not known how to optimally combine these treatments as there is an infinite number of possible administration schedules. We used mechanistic mathematical modeling and mouse modeling to identify a substantially superior administration schedule to those currently being used in clinical trials.

**Methods:** We developed an ordinary differential equation-based mechanistic mathematical model of tumor response to PARPi/radiation combination therapy (PARPi + RT). The model accounts for tumor cell proliferation, radiation-induced DNA damage-dependent cell death or quiescence, the dynamics of DNA damage repair, the inhibition of DNA damage repair by the PARPi and the pharmacokinetics of the PARPi. We used the probabilistic programming language Stan to develop a framework for Hamiltonian Monte Carlo-based hierarchical Bayesian inference for parameter estimation. We fit our model to longitudinal magnetic resonance imaging data of response of a genetically engineered glioblastoma mouse model to control, PARPi, RT and PARPi + RT. We (retrospectively) validated the functional form of the model using longitudinal tumor volume data from different glioblastoma mouse models treated with different schedules of PARPi, RT and PARPi + RT. We then used the validated model to compare different possible dosing schedules, within toxicity and feasibility constraints, and obtain a schedule predicted to

be substantially superior to those currently undergoing clinical evaluation. The superiority of our novel schedule is currently being validated in a preclinical trial.

**Results:** Our model fit the longitudinal imaging data well. It also successfully predicted the treatment response of all published preclinical studies of glioblastoma response to PARPi, RT and PARPi + RT with longitudinal tumor volume data available, irrespective of the mouse model or schedule used. Our model predicts that the dose of the PARPi and the time interval between PARPi and RT administration have large effects on survival. Current schedules administer PARPi twice daily with no specified time interval between PARPi and RT administration. We predict that once daily higher dose administration of PARPi will be superior to the twice daily lower dose schedule. We also predict that a short time interval between PARPi and RT administration (approximately 1 hour) is vital to achieve radiation sensitization.

**Conclusions:** We used mathematical modeling of longitudinal imaging data of a genetically engineered glioblastoma mouse model to establish a novel PARPi + RT schedule predicted to be substantially superior to currently employed schedules. Prospective evaluation of the schedule in a preclinical trial is in progress. If successfully validated, we will translate the novel schedule from mice to humans for evaluation in future clinical trials of PARPi + RT.

## Implicit versus explicit control strategies in models for vector-borne disease epidemiology

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Throughout the vector-borne disease modeling literature, there exist two general frameworks for incorporating vector management strategies (e.g. area-wide adulticide spraying and larval source reduction campaigns) into vector population models, namely, the “implicit” and “explicit” control frameworks. The more simplistic “implicit” framework facilitates derivation of mathematically rigorous results on disease suppression and optimal control, but the biological connection of these results to real-world “explicit” control actions that could guide specific management actions is often vague. In this talk, we formally define the biological and mathematical relationships between implicit and explicit control, and we provide mathematical expressions relating the strength of implicit control to management-relevant properties of explicit control for common intervention strategies. These expressions allow optimal control and sensitivity analysis results in existing implicit control studies to be interpreted in terms of real world actions. Our work reveals a previously unknown fact: implicit control is a meaningful approximation of explicit control only when resonance-like synergistic effects between multiple controls have a negligible effect on average population reduction. When non-negligible synergy exists, implicit control results may fail to provide accurate predictions regarding vector control and disease spread. The methodology we establish can be applied to study the interaction of phenological effects with control strategies, and we present a new technique for finding impulse control strategies that optimally reduce a vector population in the presence of seasonally oscillating model parameters. Our work builds an effective bridge between analytically interesting and mathematically tractable implicit control and the mathematically challenging, action-oriented explicit control.

## RULE-OF-FIVE

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There is broad agreement among educators that more mathematical modeling should be incorporated into the undergraduate biology curriculum, but efforts to achieve this goal are hampered by the lack of a clear conceptualization of what mathematical modeling is. In this talk, we offer a conceptualization based on an extension of the “Rule of Four” initially used in calculus reform to a “Rule of Five” (Diaz Eaton *et al.*, 2019). We then illustrate this conceptualization with an example module that looks at density-dependent growth through a multi-faceted exploration involving a physical simulation, a computer simulation, data, graphs, and formulas.

## Quantifying Insulin Sensitivity in Obese Adolescent Girls

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Insulin sensitivity (SI) decreases during adolescence and is prevalent in obese adolescent girls. In order to study SI under physiological conditions, researchers have developed a method of using glucose and insulin concentrations obtained from an oral glucose tolerance test (OGTT) with the Oral Minimal Model (OMM), a differential-equations based mathematical model of glucose-insulin dynamics that estimates SI. This method for analyzing SI was developed in adults where glucose and insulin levels typically return to baseline within two or three hours, thus adaptations to the model were needed for application in adolescents. To assess SI in adolescents, we administered a frequently sampled OGTT to a cohort of 75 obese adolescent girls in the 95th percentile or higher body mass index with an average age of 16 years. In this highly insulin resistant population, the standard 2 hour OGTT had to be extended to 6 hours to allow participants' glucose and insulin concentrations to return to baseline. To investigate how measures of SI change with protocol duration, we compared SI values computed using an OMM fit to six hour OGTT data to SI values computed using OMMs fit to data collected over shorter durations. Specifically, we considered two, three and four hour implementations of OMMs. We found that shorter protocols produce SI values that overestimate SI computed with a six hour protocol with a bias up to -73.5% illustrating that OGTT-OMM protocol duration affects SI estimates. Future work may exploit these insights to establish methodologies to reliably estimate SI in adolescents from shorter OGTT protocols that are less time and resource intensive compared to the six hour protocol. These methodologies will facilitate characterization of SI in individual patients as well as in different disease conditions, such as diabetes and metabolic syndrome, and may support the development of targeted therapeutic approaches.

## Inflammatory-thermal-pain-cardiovascular interactions during a pathogen challenge

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In life-threatening systemic inflammatory response syndromes, such as sepsis, an uncontrolled infection leads to the spread of excessive inflammation throughout the body. Sepsis is one of the leading causes of death worldwide, and symptoms include a high fever, very low blood pressure, and abnormally rapid heart rate. The treatment of sepsis is challenging and inflicts sizable costs on the US healthcare system, as this condition is one of the five illnesses associated with the most expensive hospital stays. A lot remains unknown about the processes involved in sepsis and the ways by which systemic inflammation correlates with hemodynamics. This study uses mathematical modeling to explore mechanisms for interaction between the inflammatory, pain, thermal, and cardiovascular systems. To do so, we develop a physiological mathematical model for each subsystem, proposing mechanisms for their interplay. To test our model, we use data from two independent clinical studies on the human response to a bacterial toxin. In addition, we set up a simulation analysis to determine if the model is valid under pathological conditions in order to ensure that it can capture the effects of common treatments, such as antibiotics, antipyretics, and vasopressors. Finally, we conduct a therapy study combining all three medications. Our results show that the most favorable recovery outcome is achieved by the multimodal treatment, which simultaneously targets the pathogen as well as the infection symptoms of fever, pain, and lowering vascular resistance.

## Effects of TCR-specific thymic output and proliferation on naive T cell clone abundance distributions

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The set of T cells that express the same T cell receptor (TCR) sequence represent a T cell clone. The number of different clones reflects the number of different TCRs arising from stochastic recombination of the V(D)J gene segments during T cell development in the thymus and is an important factor in immune function. Overall, recombination rates are not the same for all sequences, leading to biases in certain TCRs. Moreover, clone-dependent interactions between TCRs and self-antigens are known to trigger proliferation and sustain naive T cell survival. These clone-specific effects are expected to influence the clone abundance distributions or clone counts (the number of different clones that are represented by a specific number of cells) that measures the diversity of naive T cell receptors in an organism. Using a mean-field approximation to the solution of a regulated birth-death-immigration model, we systematically investigate the effects of TCR-dependent heterogeneity in both T cell production and proliferation rates on the overall clone abundance distributions. We quantify how heterogeneity in sequence-specific thymic output and proliferation rates affect the shape of the clone abundance distribution. By comparing predicted clone abundances derived from our heterogeneous birth-death-immigration model with experimentally sampled clone abundances, we quantify the heterogeneity necessary to generate the observed abundances. Our findings indicate that heterogeneity in proliferation rates is more likely the mechanism underlying the observed clone abundance distributions than heterogeneity in immigration rates.

## **Investigating the sequence composition of core promoter elements in *Drosophila* and human using a computational analysis**

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Transcription of protein-coding genes in eukaryotes is controlled by the RNA polymerase II system. A key component in the initiation of transcription in this system are the core promoter element (CPE) sequences, including the Initiator (INR), which is thought to be involved in the recruitment of RNA polymerase II. In this study, we investigate the sequence composition of the INR at experimentally defined promoter regions in *Drosophila melanogaster* and *Homo sapiens*. Using computational and statistical methods, including modified position weight matrix (PWM)-based methods in our MARZ algorithm as well as the commonly used MAST algorithm, we examine the significance of individual nucleotides and potential interdependencies between nucleotides within these sequences. The results will improve our ability to predict the location and potential regulatory contribution of the CPEs at promoters.

## Numerical Error in Model Selection for Biochemical Systems

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We present a model selection study of biochemical systems with a focus on the influence of numerical error. Model selection methods use a variety of information theory based criteria that measure the distance from the probability density function (pdf) of a possible model to the pdf of the actual phenomenon. These model selection criteria essentially balance model complexity with goodness-of-fit, often measured in the maximum likelihood (or least-squares) sense. There are a variety of sources of noise including measurement error, stochastic variability, and numerical error in approximating the solution to the model. The last source of noise, numerical error, is often noted in passing. Here we investigate the numerical error arising from different numerical schemes used to solve the models. We build upon previous work with the goal of helping practitioners to identify when numerical error is the primary source of error in the model selection procedure.

## Modeling the circadian effects of mood

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Mental health disorders are the leading global cause of disability, affecting more than 300 million people worldwide and forming a major contribution to the overall global burden of disease. Building dynamic models of mood based on physiological data presents a number of interesting challenges, due in part to the discrepancies between available physiological measurements and the nature of self-reported mood. Improved understanding of the physiological drivers of mood regulation could profoundly expand the suite of potential treatment strategies for mood disorders. Current work using longitudinal data of human subjects working on shift schedules shows a strong link between the central circadian pacemaker and mood regulation, and there are a variety of clinical studies linking circadian dysregulation to major psychiatric syndromes. There has been success modeling and classifying the time course of self-reported measures of mood using discrete time Markov chains in specialized populations, however this framework has not yet been used to examine the effects of circadian disruption. Here, we extend an existing framework to study the long term effects on mood in a population of shift workers due to sleep deprivation, circadian dysregulation, and a suite of other physiological metrics. This work takes advantage of continuously measured wearable technology to generate high dimensional time series of heart rate, sleep, and mood in each individual, providing a unique opportunity to examine dynamic changes in mood as a function of sleep patterns and estimated circadian phase.

## Dynamics of PAR Proteins Explain the Oscillation and Ratcheting Mechanisms in Dorsal Closure

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We present a vertex-based model for *Drosophila* dorsal closure that predicts the mechanics of cell oscillation and contraction from the dynamics of the PAR proteins. Based on experimental observations of how aPKC, Par-6, and Bazooka translocate from the circumference of the apical surface to the medial domain, and how they interact with each other and ultimately regulate the apicomедial actomyosin, we formulate a system of differential equations that captures the key features of dorsal closure, including distinctive behaviors in its early, slow, and fast phases. The oscillation in cell area in the early phase of dorsal closure results from an intracellular negative feedback loop that involves myosin, an actomyosin regulator, aPKC, and Bazooka. In the slow phase, gradual sequestration of apicomédial aPKC by Bazooka clusters causes incomplete disassembly of the actomyosin network over each cycle of oscillation, thus producing a so-called ratchet. The fast phase of rapid cell and tissue contraction arises when medial myosin, no longer antagonized by aPKC, builds up in time and produces sustained contraction. Thus, a minimal set of rules governing the dynamics of the PAR proteins, extracted from experimental observations, can account for all major mechanical outcomes of dorsal closure, including the transitions between its three distinct phases. In more recent work, the modeling framework developed is applied to *Drosophila* salivary gland tubulogenesis in which complex cell shape changes result in the formation of invaginated tubes within the embryo.

## Comments and discussion on modeling time since infection

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We will conclude the mini-symposium by commenting briefly on talks from both sessions, and guiding a discussion on *applications* of models that account for time since infection. These models are intended to provide more accurate representations of biology, and often present interesting mathematical challenges. But under what circumstances do we *need* to account for dependence of epidemiological processes on time since infection? When exploring dynamics? When designing control interventions? When fitting models to data? ...

# The Combination of Seasonal Variations and Direct Disease Transmission in A Mathematical Model of Nosemosis Can Lead to Chaos in the Hive

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Nosemosis is a common disease of the Western honeybee (*Apis mellifera*) that is caused by the microsporidian parasites *Nosema apis*, and more recently and more virulently, *N. ceranae*. Mathematical models of *N. ceranae* infestations have been proposed previously: Betti et al, 2014, focused on direct transmission of the disease, whereas Petric et al, 2017, emphasised an indirect transmission route. Both models were based on the cast-structured honeybee population model of Khoury et al, 2017. We present a model that accounts for both transmission routes. Like Petric et al, 2017, and Ratti et al, 2017, it also accounts for seasonal variations in honeybee population biology. The resulting model is a non-autonomous system of 5 ordinary differential equations with periodic coefficients. The analytical accessibility of this model is limited, wherefore we resort to computational exploration. Careful simulations of the model suggest that for some range of disease transmission rates the interplay of seasonal variations and direct disease transmission can lead to period doubling and chaos, whereas for larger values of the direct disease transmission rate the colony will fail, whereas for smaller values the combined effects of both transmission routes determine longterm behaviour.

**References:** Betti et al, PlosOne 9(10): e110237. doi:10.1371/journal.pone.0110237, 2014; Khoury et al, PlosOne 6(4): e18491. doi:10.1371/journal.pone.0018491, 2011; Petric et al, J. Biol. Dyn. 11(S2):348-378 doi: 10.1080/17513758.2016.1237682, 2017; Ratti et al, Bull. Math. Biol. 79(6):1218-1253 doi: 10.1007/s11538-017-0281-6, 2017

## Identifiability, uncertainty, & parameter reduction in mathematical epidemiology

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The interactions between parameters, model structure, and outputs can determine what inferences, predictions, and control strategies are possible for a given system. Identifiability, estimability, and parameter reduction methods are thus essential for many questions in mathematical modeling and uncertainty quantification. These approaches can help to determine what inferences and predictions are possible from a given model and data set, and help guide control strategies and new data collection. In this talk, we will discuss methods for identifiability and estimability analysis, and examine some of the potential difficulties in estimating the effectiveness of interventions in infectious diseases. We will illustrate how reparameterization and alternative data collection may help resolve various types of unidentifiability and allow for successful intervention predictions.

## Immune system changes with age and age-dependence of cancer survival time from diagnosis

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The immune system changes over an individual's lifetime, most notably through thymus involution. Age-dependence in counts, percentages, and functionality of immune cells potentially involved in cancer control, including T cells, dendritic cells, and natural killer cells, has been noted. The theory that decline in immune surveillance effectiveness explains the rising incidence of many cancers with age currently competes with the theory of cumulative mutations. Both mechanisms may play a role. However, apart from cancer incidence, cancer survival time from diagnosis also decreases with age, even when other significant factors such as primary tumor size at diagnosis are taken into account. Immune system changes with age may be an explanatory factor. It is not known whether this can be attributed to a decline in the naive T cell repertoire causing a decrease in the probability of an adaptive anti-tumor response being existent, or to other trends in immune cell counts and functionality with age that quantitatively change either adaptive or innate anti-tumor responses. Moreover, significant gender differences have been found in both cancer survival time from diagnosis and immune system aging. Here, a model for tumor-immune interactions originally developed by Robertson-Tessi et al (2012) is expanded to account for age-dependencies relating to several immune cell types. Data from the NCI SEER Database are modeled. Most age-related trends in immune cells are fairly linear with age, yet survival time from cancer diagnosis shows a definite nonlinear dependence, with a notably greater decline starting in the seventh decade of life, and for some cancer types a degree of non-monotonicity in the first three decades. The model is used to assess the extent to which this nonlinear dependence might be explained by the effect of immune system age-dependence on tumor-immune interactions.

## Understanding the effect of temperature on Bluetongue disease risk in livestock

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### **Presenter: Fadoua El Moustaid**

Vector-borne diseases (VBDs) cause major threats to humans and animals and are very difficult to manage. The transmission of VBDs is governed by complex interactions including pathogen characteristics, vector-host interactions, and environmental conditions. Bluetongue viral (BTV) disease is a midge-borne disease threatening animal agriculture and the economy of affected countries. As with any emerging disease, it is difficult to predict transmission pathways. Using modeling tools, we can predict where transmission can occur based on suitable temperatures for BTV. Here, we fit the midge life history traits that are sensitive to temperature using a Bayesian model. Then, we derive a new basic reproductive number  $R_0$  formula that incorporates midge traits response to temperature variations. Our results show that outbreaks of BTV can occur between 21.5°C and 30.7°C with peak transmission at 28°C. The greatest uncertainty in  $R_0$  is associated with the mortality and fecundity of midges at peak transmission, midges probability of becoming infectious post infection at the lower edge of the thermal range, and the biting rate together with vector competence at the higher edge of the thermal range. We compare our  $R_0$  to two other  $R_0$  versions and we show that incorporating thermal curves in all three formulas lead to similar predictions.

# Informing Cancer Treatment Decisions Using Spatial Evolutionary Game Theory

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**BACKGROUND:** Prostate cancer is characterized by complex interactions between tumor cells and stromal elements in the tumor microenvironment. These interactions are critical for the survival and proliferation of the cancer, especially under therapeutic pressure. While some previous modeling efforts have considered space, the creation of a three cell population spatial analytical model for population dynamics is novel in the field of oncology.

**METHODS:** We develop a spatial approximation of tumor growth using an ODE model comprised of modified replicator equations resulting from pair-approximation on a regular graph (the Ohtsuki-Nowak transform). We model the population dynamics of a tumor taking into consideration the interactions between fibroblasts, stromally-dependent, and -independent cells. We solve the ODE for population regimes under various clinical circumstances. We investigate different model features including different update rules and different neighborhood size to study generalizable features of these population dynamics. We then compare results from the model with published descriptions of disease course to analyze potential therapeutic decisions related to our model.

**RESULTS:** Using our model, we explore a number of key decision points in the treatment of metastatic prostate cancer. We consider therapeutic agent choice and treatment timing, and present possibilities for treatment optimization, as well as suggesting treatment choices which modify the interactions themselves, not just the tumor cells.

**CONCLUSION:** As prostate cancers, and other solid tumors, are necessarily spatially heterogeneous, the inclusion of these spatial aspects in an analytical model of three cell tumor cell populations is critical in the development of optimized therapeutic strategies for metastatic prostate cancer. The choice between cytotoxic and stromal disrupters, as well as treatment initiation and duration, can be informed using a spatial model.

# Absolutely Robust Control Modules in Chemical Reaction Networks

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We use ideas from the theory of absolute concentration robustness to control a species of interest in a given chemical reaction network. The results are based on the network topology and the deficiency of the system, independent of reaction parameter values. The control holds in the stochastic regime and the quasistationary distribution of the controlled species is shown to be approximately Poisson under a specific scaling limit.

# Mathematical oncology approaches to identify optimal dose, time and target of cancer radiation therapy for robust immune activation

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Radiation therapy (RT) is the single most utilized therapeutic agent in oncology, yet advances in radiation oncology have primarily focused on physical properties of the radiation beam. One obvious shortcoming of current one size fits all clinical practice is that RT is planned without regard to any of the tumor-environmental factors that may influence outcome. An extensive body of literature has emerged relating to the immune-activating ability of RT. In fact, RT efficacy may be a combination of the direct cytotoxic effect of radiation and, possibly more importantly, the subsequent indirect effect of stimulating a successful antitumor immune response. Yet, current RT fractionation has not specifically focused on enhancing immune responses despite evidence that fewer, larger doses induce significantly stronger antitumor immunity. Daily RT over many weeks may even be detrimental to antitumor immunity, as immune cells are generally very radiation sensitive. Understanding the complex, non-linear cytotoxic and immunologic consequences of radiation is of high biological interest and clinical value. We have developed a variety of mathematical and computational models to quantify tumor-immune interactions, and to determine RT dose, time and target in metastatic disease that optimize RT-induced immunity. Coupling mathematical models of local tumor-immune dynamics and systemic T cell trafficking allows us to simulate the evolution of tumor and immune cell populations in anatomically distant sites following local therapy and thus computationally evaluate immune interconnectivity. Model simulations suggest that the most immunogenic RT target is in organs with low blood flow fractions, and that optimal doses to maximize anti-tumor immunity are between 10 and 13 Gy. In combination therapy, RT prior to surgery may induce significantly stronger antitumor immunity than RT after surgery. Our innovative models based upon interactions of the tumor with its immune-environment may elucidate new treatment strategies that improve tumor control and protect normal tissues.

## Anti-leukemic stem cell compounds: *in silico* and *in vitro* screening.

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Approximately 70% of acute myeloid leukemia (AML) are refractory to therapy and this is at least partially driven by the chemo-resistant nature of the leukemic stem cells (LSCs) that sustain the disease. Current methodologies to identify chemotherapeutic agents effective in AML are based upon readouts of general toxicity in the bulk of leukemic cells, and thereby (paradoxically) exclude LSCs and their unique features such as long-term self-renewal. Thus, novel approaches to identify therapeutics that effectively target LSCs may yield major improvements in care, either alone or in combination with standard of care therapy. We performed *in silico* analysis of human LSC gene expression signatures using existing datasets of drug-gene interactions to identify compounds predicted to target LSC gene programs and spare normal cells. We followed this with a novel *in vitro* LSC assay to identify drugs that effectively eliminate human AML LSCs. Our study demonstrates the efficacy of combining computational analysis of stem cell gene expression signatures with *in vitro* screening to identify novel compounds that target the therapy-resistant LSC at the root of relapse in AML.

## Characterizing *C. difficile* toxin production through networks and mechanistic mathematical modeling.

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The main virulence factors in *C. difficile* infection are toxins, yet little is known about the specific mechanism leading to it. In recent years, new technology has allowed us to achieve measurements of hundreds of metabolites and the expression of thousands of genes which maybe crucial to understand the driving factors in *C. difficile* colonization and toxin production. It is believed that toxin production is mediated by competition for nutrients in the gut metabolome, which makes the large-scale metabolomics data useful. However, with these high-dimensional ‘omics’ data comes a critical need to reduce these datasets to their most functional elements to elucidate the key components driving toxin production. Networks are common tools for analyzing these data, however, at times graphical networks can be overwhelming due to the complexity of the information. Specifically, current techniques used to analyze omics data are not designed to support parsimonious mechanistic models of bacterial pathogenesis. In this work, we use sparse graphical networks to understand correlations within our high dimensional data set. We use a recent animal model of *C. difficile* infection in which mice were antibiotic treated with cefoperazone and challenged with *C. difficile* 2 days following treatment. We develop sparse graphical networks to identify correlations between metabolites and toxins within high dimensional datasets and develop a mechanistic model of processes related to our network. We find the Stickland reaction to be critical in toxin production and suggest potential mitigation strategies for reducing toxin production.

## Agent-based model to assess public health impact of pre-vaccination screening strategy against dengue with the Dengvaxia vaccine

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The tetravalent dengue vaccine CYD-TDV (Dengvaxia) is the first licensed vaccine against dengue, but recent findings indicate an elevated risk of severe disease among vaccinees without prior dengue virus exposure. The World Health Organization currently recommends CYD-TDV only for individuals with serological confirmation of past exposure to dengue virus. Our objective was to evaluate the potential impact and cost-effectiveness of vaccination following serological screening. To do so, we simulated dengue virus transmission using a stochastic, agent-based model. With this model, we were able to realistically account for several forms of heterogeneity involved in the transmission of dengue virus. We estimated the impact of vaccination by simulating 10 years of routine pre-vaccination screening in 9-year olds, and comparing the results to a baseline scenario without vaccine. We projected the proportion of symptomatic and hospitalized cases averted as a function of the sensitivity (true positive rate) and specificity (true negative rate) of serological screening. In addition to the agent-based model assessment of direct and indirect impact of vaccination, we evaluated only the direct impact of vaccination using a mathematical model based on differential equations. Scenarios about the cost-effectiveness of screening and vaccination were chosen to be representative of Brazil and the Philippines. We found that public health impact depended primarily on the sensitivity of serological screening in high-transmission settings and on a combination of sensitivity and specificity in low-transmission settings. From a public payer perspective, pre-vaccination screening was cost-effective in scenarios with high screening sensitivity and assuming a high willingness to pay to avert a disability-adjusted life-year. Scenarios of cost-effectiveness from an individual perspective were more restricted, due to some individuals paying for screening but not benefiting from the intervention. Whereas the results of this analysis offer general guidelines about CYD-TDV vaccination, decisions in specific contexts would benefit from additional, more context-specific modeling analyses. In conclusion, vaccination with CYD-TDV following serological screening could have a positive impact in certain epidemiological settings, provided that screening is highly specific (to reduce individual harm), at least moderately sensitive (to increase public health benefits), and inexpensive.

## Unraveling the role of fibrosis in 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. Fibrosis is common in older granulomas, and has been associated with both positive and negative disease outcomes. Little is known about fibrosis in TB, partly due to the fact that fibroblasts are difficult to identify using traditional antibody-based techniques.

To provide insight into the role that fibrosis plays at a single granuloma scale, we have developed a computational, agent-based model of granuloma formation in the lung following infection with *Mtb*. In previously published work we have identified the mechanisms driving fibroblast to myofibroblast differentiation within a granuloma. Here we have extended this work to look at how other populations of cells contribute to granuloma fibrosis and how fibrosis alters granuloma architecture and the ability of a granuloma to control bacteria. Using immunohistochemistry, we have further characterized areas of fibrosis and collagen deposition in TB granulomas. Our results suggest that while resident fibroblasts contribute to early fibrosis, both fibrocytes and macrophage to myofibroblast transformation play a key role in walling off the granuloma, and that collagen deposition decreases the promotability of bacterial dissemination.

# FIELD-DATA-BASED VIRAL EPIDEMIC MODELS FOR VARROA-AFFECTED BEE COLONIES

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Models for investigating the damage caused by the ectoparasitic mite *Varroa destructor* on the honey bee *Apis mellifera* colonies are presented, [1, 2]. Mites are parasites of the beehives, indeed they suckle hemolymph from their host. But they became also vectors for the transmission of several lethal viral diseases, that are the main responsible of Colony Collapse Disorder.

Only four possible attainable equilibria are found. The healthy beehive represents the best possible outcome, with a less welcome alternative being the mite-free but endemic equilibrium, with the disease among the thriving bee population. Infected bees can also coexist with When the *Varroa* mites invade the beehive, the infected bees can coexist with the disease endemically affecting both species, or alternatively the disease will affect all the bees, driving the healthy bees to extinction.

The analysis is in line with the observations in natural honey bee colonies, where the diseases caused by varroa are endemic: if the mite population is present, necessarily the viral infection occurs. The simulations of this study are based on some parameter values that originate from a field study and are calibrated using this information.

## References

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## Fluid dynamics of vesicular transport in dendritic spines

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We model the fluid dynamics of vesicle transport into dendritic spines, micron-sized structures located at the postsynapses of neurons. Dendritic spines are characterized by their thin necks and bulbous heads, and recent high-resolution 3D images show a fascinating variety of spine morphologies. Our model reduces the fluid dynamics of vesicle motion to two essential parameters representing the system geometry and elasticity and allows us to thoroughly explore phase space. Upon including competing molecular motor species that push and pull on vesicles, we observe multiple stable solutions reminiscent of the observed behavior. We discuss whether it would be feasible for neurons could exploit such a switch to control the strength of synapses.

## Dynamics of Cerebellar Stellate Cells in Response to A Pair of Inputs

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Cerebellar stellate cells can inhibit the response of Purkinje cells, the sole output of the cerebellum. Stellate cells are (non-)responsive to stimulation of a pair of fixed excitatory and varying inhibitory pre-synaptic inputs if the magnitude of inhibition lies (within) outside a specific range. We employ a revised Hodgkin–Huxley type model to investigate switching between responsive and non-responsive dynamics upon an increase in the magnitude of excitation/inhibition. A three-dimensional (reduced) model is initially derived from the six-dimensional (original) model, and then analyzed to demonstrate that they both exhibit type I excitability possessing a saddle-node bifurcation on an invariant cycle (SNIC) with respect to the applied current. Using slow-fast analysis, we demonstrate that (i) the original model possesses three equilibria lying at the intersection of the critical manifold of the fast subsystem and the nullcline of the slow variable  $h_A$ , the inactivation variable of the A-type  $K^+$  channel, (ii) the middle equilibrium is of saddle type with a stable manifold (computed from the reduced model) acting as a boundary between the responsive and non-responsive regimes. We use the same model to also study the biphasic latency profile and the temporal decrease in excitability of these cells. The slow-fast analysis shows that the (ghost of) SNIC is formed when  $h_A$ -nullcline the nullcline associated with the slow variable is (in close proximity) tangential to the critical manifold. The slow dynamics associated with the (ghost of) SNIC and the lower stable branch of the critical manifold are responsible for generating the biphasic first-spike latency. These results provide good insights into the complex dynamics of stellate cells.

# Prey-Predator-Parasite: An Ecosystem Model With Fragile Persistence

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The recent decline and disappearance of amphibians causes much ecological concern. Previously, we examined a host-infection epidemiological model motivated by this issue and found rich dynamics. Here, we expand the model to an eco-epidemiological model by adding an additional species that predaes on both healthy and infected hosts, though is not susceptible to infection. With the expanded model, we show that a variety of global dynamics can arise, ranging from the often seen persistence of all three species, to bistability between survival and extinction of all three species, to the case where an extremely virulent pathogen can eradicate an ecosystem regardless of the actions of the predator or host.

## A new approach of modeling time-since-infection in epidemiology

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Constant state transition rates are the most common assumption in epidemiological modeling. Sojourns are exponentially-distributed as a consequence, which however is rarely if ever biologically reasonable. Creating n sub-stages with transition rates 1/nth the overall rate leads to more realistic gamma-distributed sojourns. When a more realistic distribution is needed for the infectious period, models may be structured by infection age. If multiple infections in a lifetime are possible, different states generally are needed to describe immune status. In this talk, we present a model that includes only two epidemiological states, never infected and infected at least once. That is, a single compartment includes all people who have ever been infected, with their susceptibility or infectivity being functions of time since most recent infection.

## Tracking Single Cell Chronic Myelomonocytic Leukemia Diversity Across Patients

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Chronic myelomonocytic leukemia (CMML) is an aggressive clonal hematopoietic malignancy hallmark with monocytosis, cytopenia, and marrow dysplasia. CMML biology remains poorly understood, with a 30% chance of progressing to acute myeloid leukemia, and an overall unfavorable prognosis with a median survival of 34 months—metrics which have not appreciably changed over the last three decades. Population-level variability, here termed intraleukemic heterogeneity (ILH), suggests that there are different evolutionary trajectories that shape disease progression. Currently, the only curative treatment option is an allogeneic stem cell transplant, which many patients are not eligible for due to co-morbidities and advanced age. CMML patients offer a unique opportunity to better identify molecular and cell-phenotypic predictors of evolution and therapeutic consequences of ILH in hematologic malignancies, because most patients can be longitudinally followed in a treatment naive state before they progress. To develop a toolkit to quantify this evolutionary process, we focused on individual leukemia patients' bone marrow mononuclear cell samples, in comparison to healthy subjects, to statistically describe ILH. We use a generalized diversity measure to quantify ILH, and find that it can characterize disease stage at the level of sub-population structures derived from single cell RNA sequencing. Furthermore, using single-cell, high parameter flow cytometry data, we can create nearest-neighbor graphs in a high-dimensional parameter space of patient cytokine receptor profiles. Then, we use community detection to determine phenotypically similar cells that reflect biologically meaningful phenotypes. These statistical and computational inferences lay the foundation for novel mathematical modeling techniques that seek to understand potential mechanisms underlying CMML progression and timing of clonal expansions.

## Statistical Inference for Circadian pacemaking

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Organisms have evolved an internal biological clock which allows them to temporally regulate and organize their physiological and behavioral responses to cope in an optimal way with the fundamentally periodic nature of the environment. It is now well established that the molecular genetics of such rhythms within the cell consist of interwoven transcriptional-translational feedback loops (TTFLs) involving about 15 clock genes, which generate circa 24-h oscillations in many cellular functions at cell population or whole organism levels. We will present statistical methods and modelling approaches that address newly emerging large circadian data sets, namely spatio-temporal gene expression in SCN neurons and rest-activity actigraph data obtained from non-invasive e-monitoring, both of which provide unique opportunities for furthering progress in understanding the synchronicity of circadian pacemaking and address implications for monitoring patients in chronotherapeutic healthcare.

## Fast Approximations for Stochastic Epidemic Models Fit to Partial Incidence Counts

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Stochastic epidemic models (SEMs) describe the transmission dynamics of infectious disease outbreaks. The task of fitting a SEM, often represented as a Markov jump process (MJP), is complicated by the limited extent of incidence data, which are recorded at discrete times and usually capture only a fraction of cases. The absence of complete subject-level disease histories makes analytically integrating over the missing data impossible. Furthermore, even with complete subject-level data, the computational burden of repeatedly evaluating the MJP likelihood makes it cumbersome to perform exact Bayesian inference for SEM parameters in large populations. Approximate inference via the linear noise approximation (LNA) has recently been proposed as a way of approximating the MJP transition density in the case of partially observed prevalence counts. However, analyzing partially observed incidence using the LNA is challenging since the data reflect the new infections in each inter-observation interval, while the SEM dynamics of the process are driven by the model compartment counts. We demonstrate how a reparameterization of the SEM in terms of its constituent counting processes, along with a transformation of the approximating diffusion, on which the LNA is based, can be used to adapt the LNA for fitting SEMs to partially observed incidence data. We demonstrate the method in the context of fitting a stochastic Susceptible-Infected- Recovered model to observed incidence counts, which are modelled as a negative binomial realization of the true unobserved incidence, and discuss extensions to more complex SEM dynamics.

## Calcium oscillation-dependent and -independent glycolytic oscillations in models of pancreatic beta cells

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Normal glucose-stimulated insulin secretion is oscillatory, a response mediated by the electrically active beta cells in the islets of Langerhans. Glucose triggers insulin secretion by increasing the intracellular ATP/ADP ratio via glycolysis and ATP production in the mitochondria. This in turn inhibits KATP potassium channels, leading to depolarization, electrical bursting activity, and associated calcium entry - the main stimulus for insulin secretion. Glycolysis in beta cells can be spontaneously oscillatory, as shown in islets with calcium levels clamped and in islets displaying compound bursting. Generally, however, there is significant interaction between the metabolic and electrical subsystems, and islet oscillations appear often to require their mutual interaction. The so-called dual oscillator model was developed to capture these interactions. A lineage of models based on different reductions of and modifications to the dual oscillator model have been developed, including the recent integrated oscillator model. These models can generate oscillations with varying degrees of dependence on coupling between subsystems, accounting for many experimental observations. We compare these models in terms of the underlying mechanism for these oscillations.

## Spatially Coherent Oscillations in Neuronal Networks

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Given the ubiquity of connections within and between regions of the brain, we present a general neural field model that captures a multitude of neuronal population types and types of interconnections, as well as local neuromodulation processes, such as adaptation. We analyze the generation of spatially localized oscillations due to an constantly-driven input stimulus on both 1-dimensional and 2-dimensional domains. We discuss the role that the spatial symmetries of the synaptic connections play on the spatial structure of the oscillations generated in the different neuronal populations. We expect the qualitative extension of these results to more complicated neural network models with additional biological details, in particular, heterogeneous spatial structure, synaptic depression, synaptic delays, and noise.

## Models of Chronic Hepatitis B Infection

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Chronic hepatitis B infection is a major public health burden, leading to more than 750,000 deaths per year as result of cirrhosis and hepatocellular carcinoma. Understanding the interplay between viral factors and the host immune reaction is essential for designing interventions. We develop a mathematical model of chronic HBV infection and the immune response, incorporating long-term effects such as immune exhaustion. While immune reactivation is a desired outcome that can reduce the risk of cancer development, it can also lead to heightened liver damage. We use our model to explore this tradeoff.

# Mathematical problems arising from studying daily rhythms with smartphones and wearables

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Millions of workers follow night or nonstandard shifts. A similar number of individuals travel overseas each year. This leads to misalignment of the daily (circadian) clock in individuals: a clock that controls sleep, performance, and nearly every physiological process in our body. A mathematical model of this clock can be used to optimize schedules to maximize productivity and minimize jetlag. We simulate this model in a smartphone app, ENTRAIN ([www.entrain.org](http://www.entrain.org)), which has been installed in phones over 200,000 times in over 100 countries. I will discuss techniques we have been developing and clinically testing to determine sleep stage and circadian time from wearable data, for example, as collected by our app or used in many commercially available sleep trackers. This project has lead us to develop new techniques to: 1) estimate phase from noisy data with gaps, 2) rapidly simulate of population densities from high dimensional models and 3) determine how mathematical models of sleep and circadian physiology can be used with machine learning techniques to improve predictions.

Incorporating time series at different spatio-temporal levels to understand dynamics of  
motor-cargo complexes

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Cargos, such as vesicles and organelles, are moved by multiple molecular along microtubules within cells. Understanding the dynamics of these motor-cargo complexes is crucial to gain insight on intracellular dynamics more generally. While molecular motors have been studied intensively in recent years (especially the study of individual motors), fluorescence techniques coupled to other experimental advances allow for the control of the number of motors attached to a cargo and for *in vivo* observations of cargos. Different experimental techniques allow for the collection of time series of these motor-cargo complexes at differing sampling rates. While it would seem to be most advantageous to use the fastest sampling, this also introduces certain observational artifacts. In this talk, inference for stochastic models will be discussed in the context of these varying sampling rates and experimental techniques.

## Modeling One-Dimensional Biofilms in Porous Media

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In this work we discuss multiscale biofilm models for porous media applications. We begin by constructing a single species single substrate model by first describing a 1D Wanner-Gujer biofilm model on the mesoscale. Processes included in the mesoscale model are hydrodynamics and transport of substrates in the reactor, biofilm and suspended bacteria growth in the pore space through consumption of a single, non-reproducing growth limiting substrate, attachment of suspended cells to the biofilm, detachment of biofilm cells, and cell lysis. The model is then upscale to the reactor scale. The resulting mesoscale model is described by a system of quasilinear balance laws. Through numerical simulations, we investigate the role of planktonic bacteria and attachment on reactor performance and biofilm dynamics.

We then extend the single species single substrate model framework to a multispecies multisubstrate system with a specific focus on uranium-contaminated water. Here we derive the meso- and macroscale equations, with a focus on arising complexities due to the embedded chemical reactions.

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### Hands-on teaching: Introducing math biology to life sciences graduate students

Mathematical manipulative models have had a long history of influence in biological research and in secondary school education, but they are frequently neglected in graduate education. Following the example set by the BioQUEST Curriculum Consortium, hands-on mathematical manipulative lessons help graduate students in life sciences break through prior fears to develop an appreciation for how mathematical reasoning informs biological understanding. This hands-on approach starts each section the use of physical manipulatives and then moves to derivation of mathematical relationships from core principles. This is followed by reading papers from primary literature that present mathematical models, which the students then recreate using appropriate computer software. Finally, the students are challenged to use these models to ask a new question. This course produces students ready to collaborate with mathematicians in their future research.

## Systemic dynamics of multiple metastases during adaptive therapy

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Despite the fact that heterogeneity is a major driver of treatment failure in metastatic cancer, treatment strategies often ignore tumor evolutionary dynamics. Adaptive therapy is an evolutionary treatment strategy shown to be effective in mouse studies of triple negative breast cancer and clinical trials of metastatic castrate-resistant prostate cancer. The aim is to maintain a constant tumor burden by exploiting sensitive and resistant cell competition; a lower dose is given to a shrinking tumor and a higher dose to a growing tumor. Systemic markers of tumor burden (such as PSA in prostate cancer) are often used for clinical decision-making, but details on how multiple distinct heterogeneous metastatic lesions contribute to systemic measures of burden are not well known.

Using an off-lattice agent-based model, we simulate continuous or adaptive strategies using an anti-proliferative drug on different metastatic tumor compositions. Assuming a tradeoff between fast proliferation and drug resistance, we investigate how number, size and spatial heterogeneity of multiple metastatic lesions affects response to adaptive therapy. We identify how these variables affect drug cycle times and time to recurrence, and when alternate interventions are needed. There is no one-size-fits-all treatment strategy for metastatic disease - multiple heterogeneous lesions can respond differently to systemic treatments. Using this computational model, we aim to better understand the underlying system of lesion responses from biomarkers of burden during evolutionary-guided treatment cycles.

## Effects of Travel Frequency on Malaria Persistence

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Travel frequency varies significantly from person to person due to occupation, age, gender, income and other factors. Only a small proportion of people travel frequently while most travel occasionally. In this talk, I will present a two-group multipatch malaria model where the human population in each patch is divided into four classes based on travel frequency and health status. The basic reproduction number is defined which governs the global dynamics of the model system. We use both analytical and numerical methods to demonstrate that the model without considering the travel difference of humans mostly underestimates the transmission potential. Numerical examples are given to further investigate the effects of travel frequency on the spread and control of malaria.

# Detecting Early Warning Signal of Complex Diseases Based on Dynamical Network Biomarkers

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Complex diseases occur under the joint action of many factors, such as multiple genes, multiple mutations of a gene, the genetic model is relatively complex. The sudden deterioration of some complex diseases is called critical state. Before the critical state comes, the condition changes slowly, and after the state, the condition deteriorates rapidly within a short time, making the treatment more difficult, the survival time becomes shorter, and the harm is great. How to diagnose the critical state in time and identify the warning signs before the disease suddenly worsens is particularly important. With influenza a as the research focus, this paper applied Dynamical Network Biomarkers (DNB) to protein sequences, constructed early warning indicators, and identified the pre-outbreak status of influenza a in 10 countries. The influenza subtypes related to the outbreak were captured through the early warning indicators. Starting from the gene expression data of a/H1N1 and H3N2 diseases, the DNB method was improved to screen the dominant gene network and identify the pre-disease state of different H1N1 subtypes.

## Transmission Dynamics and Optimal Control of Stage-structured HLB Model

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Huanglongbing (HLB) is one of the most common widespread vector-borne transmission diseases through psyllid, which is called a kind of cancer of plant disease. In this talk, according to transmission mechanism of HLB, a stage-structured model with prevention and control is introduced. A threshold value is established to measure whether or not the disease is uniformly persistent. Moreover, applying the optimal control theory, we obtain an optimal integrated strategy. Finally, in order to find the parameters of the model, we use our model to fit the data of the numbers of infected citrus trees in “Yuan Orchard”, located in Ganzhou City, Jiangxi Province in the southeast of China.

## Using Homogenization to Estimate Random-Walk Motility from Telemetry Data in Heterogeneous Landscapes

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The availability of land classification data sets and GPS location data has greatly impacted ecological studies. However, incorporating this data into meaningful spatial models can be challenging. Ecological diffusion models connect animal movement to heterogeneous landscapes through motility parameters (constants with units of area/time). Combining ideas from resource selection analysis and a homogenization technique for ecological diffusion, we devise a way to estimate motilities from land cover and GPS location data. We test this method with simulations and then apply it to mule deer movement data collected in Utah.

## Robust Versus Personalized Optimization of Cancer Immunotherapy

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\* Presenter

Mathematical models of biological systems are often validated by fitting the model to the average of an often small experimental dataset. Here we ask the question of whether predictions made from a model fit to the average of a dataset are actually applicable in samples that deviate from the average. We will explore this in the context of a mouse model of melanoma treated with two forms of immunotherapy: immune-modulating oncolytic viruses and dendritic cell injections. We have hierarchically developed a system of ordinary differential equations to describe the average of this experimental data, and optimized treatment subject to clinical constraints. Using a virtual population method, we explore the robustness of treatment response to the predicted optimal protocol; that is, we quantify the extent to which the optimal treatment protocol elicits the same qualitative response in virtual populations that deviate from the average. We find that our predicted optimal is not robust and in fact is potentially a dangerous protocol for a fraction of the virtual populations. However, if we consider a different drug dose than that used in the experiments, we are able to identify an optimal protocol that elicits a robust anti-tumor response across virtual populations. We will end by exploring how robustness influences the personalization of treatment protocols for individual mice.

## A density dependent reaction-diffusion model to study the dynamics of Nitric Oxide in a growing biofilm

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One of a number of critical roles played by  $NO\bullet$  as a chemical weapon (generated by the immune system) is to neutralize pathogens. However, the virulence of pathogens depends on the production activity of reductants to detoxify  $NO\bullet$ . Broad reactivity of  $NO\bullet$  makes it complicated to predict the fate of  $NO\bullet$  inside bacteria and its effects on the treatment of any infection. Here, we present a mathematical model of biofilm response to  $NO\bullet$ , as a stressor. The model is comprised of a PDE system of highly nonlinear reaction-diffusion equations that we study in computer simulation and determine the positive and negative effects of key parameters on bacterial defenses against  $NO\bullet$ . From the reported results, we conjecture that the oscillatory behavior of  $NO\bullet$  under microaerobic regime is a temporal phenomenon and does not give rise to a spatial pattern. It is also shown computationally that decreasing the initial size of the biofilm colony negatively impacts the functionality of reducing agents that deactivate  $NO\bullet$ . Whereas nutrient deprivation results in the development of biofilms with heterogeneous structure, its effect on the activity of  $NO\bullet$  reductants depends on the oxygen availability and biofilm size.

## Applications of an epidemiological model structured by time-since-last-infection

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The familiar SIR model that is often attributed to Kermack and McKendrick (Proc R Soc London A; 1927; 115:700-21) results from their more general time-since-infection model assuming that people recover at a constant rate, whereupon the infectious period is exponentially distributed. That mathematically convenient, but biologically unrealistic assumption characterizes much of the subsequent infectious disease modeling literature. If infected people become infectious at a constant rate, the exposed period in SEIR models also is exponentially distributed. Alfaro-Murillo (Dissertation, Purdue Univ, 2013) introduced a model structured by time-since-last-infection and explored its solution properties. To determine if his model more faithfully describes the dynamics of particular infectious diseases, whereupon it might provide a more accurate tool for assessing the impact of public health interventions, we compare results with those from conventional models.

## Modeling of combined Drug-Radiation treatment regimen in Non-Small Cell Lung Cancer

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Mathematical modeling has played an important role in developing hypotheses to be tested in clinical trials using radiation therapy and for optimizing their design. Especially in the area of accelerated fractionation and hypofractionation, radiobiological models have played a central role in trial design and estimating the therapeutic benefit.

However, the increasing complexity of treatment regimen and the use of targeted biological agents in combination with radiotherapy have emphasized the need for approaches encompassing the entire treatment, not only radiotherapy.

This session will review approaches to model cancer treatment beyond radiation therapy. It will introduce how to account for the interaction of biological agents chemotherapy with radiation using mechanistic models, and show applied examples. Furthermore, we will review nascent approaches to simulate the interaction of immunotherapy with other therapeutic approaches, and explore various methods to assess the state of the patients immune response to individualize those models.

## Math Fundamentals: One Model at a Time

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Motivation and engagement are crucial for math class success. Our world needs people with the quantitative and logical skills that math courses can provide. Linking mathematical concepts with approachable biological examples sparks student interest and inspires a depth of understanding. These links can be part of standard mathematics courses, or they can make up an entire course of their own. This talk includes several examples, along with student responses and successes.

## The impact of mosquito population dynamics on the evolution of malaria parasites

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\*Presenter

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Mosquito-borne parasites must succeed at three scales to persist: proliferating to sufficient numbers to be transmitted from host to vector in a blood meal, establishing and persisting in short-lived mosquitoes, and transmitting back to hosts. Mosquito abundance can undergo dramatic seasonal and human-induced changes, but predicting parasite evolutionary responses to those changes requires integrating parasite success across scales. We develop a data-driven model of human malaria infections to examine the evolution of a within-host trait—how parasites allocate host resources to within-host proliferation versus onward transmission—that influences disease severity and transmission success. We find that a trade-off between early and late infectiousness emerges naturally from the biology of within-host infections, where rapid proliferation—and hence limited transmission investment—enhances early infectiousness. Critically, this trade-off renders the evolution of transmission investment sensitive to ecology outside the host, which alters the value of host infectiousness at different infection ages. The expansion of a human epidemic selects strongly for early infectiousness, overwhelming the impact of host recovery rates and mosquito population dynamics. However, predicting evolutionary outcomes in response to changing ecology requires understanding any association between parasite allocation and host recovery, presently unknown. Our study shows that ecology outside the host can have a dramatic influence on the evolution of parasite traits expressed within a host, with the potential to alter both disease severity and spread.

## Cancer-immune ecology, treatment resistance and the role of within patient cellular variability

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As in the evolutionary ecology of plants and animals, populations of cancer and immune cells are structured by innate and inducible variation in morphology, resistance to attack and activity. Within tumors, cancer cell vary in the how much their proliferation and survival is to environmental stimuli. This variation is a key determinant of patients' responsiveness to chemotherapy, because evolutionary selection pressures and environmentally induced trait plasticity drives the development of drug resistant cells. Similarly, variation in the activation state of immune cells can determine the immune system's ability to regulate tumor growth. Finally, there is also an interplay between cancer and immune cell variability which will govern patients' responsiveness to novel immunotherapies.

We show how theoretical insights from evolutionary population ecology can guide the development of dynamic models of: a) the evolution of the variability of drug resistance within tumors and b) the activity and capacity of immune cells to interact with cancer cells and to regulate tumor growth. This also allows us to describe the interplay between cancer and immune cell variation and how it impacts cancer-immune ecology. These models provide insights into how therapeutic resistance emerges and how phenotypic variation could be utilized to identify patient responsiveness to therapy or to improve disease management.

## A model for the treatment and competition of malaria parasite strains

Margaret Grogan<sup>a</sup> (Presenter) and Olivia Prosper<sup>b</sup>

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We develop an ODE compartment model to investigate the effects of treatment pharmacokinetics and pharmacodynamics on the spread of drug-resistant malaria. This model is an extension of the Ross-MacDonald model for malaria transmission in which we incorporate treatment compartments into an SIRS-SI model framework for vector-borne diseases. Due to parasite mutation, selection pressure from available drug treatments, and adherence to treatment regimens, drug-resistant malaria strains have emerged and become more prominent over time. Hence, we explicitly incorporate infection due to a sensitive and a resistant strain of the malaria parasite that account for changing drug concentrations and parasite densities within treated individuals. We discuss the competition between these two strains. Since resistant strains are harder to treat, we include two disease-induced mortality parameters in the human population for the corresponding sensitive and resistant strains. In the model, the compartments are categorized by malaria strain-type infection and treatment status. The treatment stage is broken up into  $n$  compartments through which individuals progress as the drug concentration and parasite density in their system declines after being treated. It is of interest to note that the competition between these two strains may depend on the number of treated compartments. We investigate this dependency for several values of  $n$ .

## Mixed volumes of steady-state systems

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The steady-state degree of a chemical reaction network is the number of complex solutions to the steady-state system for generic parameters. In general, the steady-state degree may be difficult to compute, but it can be bounded above by the mixed volume of the system. In this presentation, using tools from combinatorial polyhedral geometry, we compute the mixed volume for three infinite families of networks, each generated by joining smaller networks to create larger ones. Each of these examples illustrate a different relationship between the steady-state degree and the mixed volume of the steady-state system.

## Non-resource effects of foundation species in marine meta-ecosystems

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Marine mussels are habitat-forming foundation species. They drive the slow accumulation of matter that feeds back on their structural stability. This non-resource effect of matter on ecosystems can lead to disturbances and to pulsed release and transport of matter over regional scales. However, non-resource effects of such endogenous pulses of matter on meta-ecosystem stability and function remain largely unknown. Using a 2-patch meta-ecosystem model of mussel bed dynamics, we show that non-resource effects of matter on the structural stability of mussel beds promote pulsed ecosystem dynamics. These pulsed fluctuations explain the maintenance of meta-ecosystem heterogeneity through out-of-phase synchrony and asynchrony over a broad range of connectivity. These regimes of spatial (a)synchrony explain a trade-off between the regional retention of matter (ecosystem function) and meta-ecosystem stability. These results reveal how foundation species can cause local and catastrophic changes that can promote regional asynchrony and stability, even under strong connectivity.

# An Immuno-Epidemiological Vector-Host Model with Within-Vector Viral Kinetics

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A current challenge for disease modeling and public health is understanding pathogen dynamics across scales since their ecology and evolution ultimately operate on several coupled scales. This is particularly true for vector-borne diseases, where within-vector, within-host, and between vector-host populations all play crucial roles in diversity and distribution of the pathogen. Despite recent modeling efforts to determine the effect of within-host virus-immune response dynamics on between-host pathogen transmission, the role of within-vector viral dynamics on disease spread is overlooked. Here we formulate an age-since-infection structured model, where epidemic model parameters are governed by ODE systems, describing within-host immune-pathogen dynamics and within-vector viral kinetics. We define the basic reproduction number,  $\mathcal{R}_0$ , and analyze the threshold dynamics of the system. Numerical results suggest that within-vector viral kinetics may play a substantial role in epidemics. Finally, we address how the model can be utilized to better predict the success of control strategies such as vaccination, drug treatment, and Wolbachio-based biocontrol.

## Long-lasting insecticidal nets and the quest for malaria eradication: A modeling approach

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The widespread use of indoors residual spraying (IRS) and long-lasting insecticidal nets (LLINs) has led to a dramatic reduction of malaria burden in endemic areas (with most of the gains attributed to the use of LLINs). Unfortunately, such heavy usage has also resulted in the challenging problem associated with the emergence of vector resistance to nearly every currently-available agent used in the insecticides. Thus, it is imperative to design malaria control strategies, based on using these (insecticides-based) interventions, that reduce malaria burden while effectively managing insecticide resistance in the mosquito population. This talk is based on using a new mathematical model for assessing the population-level impact of wide-scale use of currently-available LLINs on current global effort to eradicate malaria by 2040.

## On the Mean Speed of Bistable Transition Fronts in Unbounded Domains

Hongjun Guo<sup>a</sup> (speaker), François Hamel<sup>b</sup>, and Wei-Jie Sheng<sup>c</sup>

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In this talk, we concern with the existence and further properties of propagation speeds of transition fronts for bistable reaction-diffusion equations in exterior domains and in some domains with multiple cylindrical branches. In exterior domains we show that all transition fronts propagate with the same global mean speed, which turns out to be equal to the uniquely defined planar speed. In domains with multiple cylindrical branches, we show that the solutions emanating from some branches and propagating completely are transition fronts propagating with the unique planar speed. We also give some geometrical and scaling conditions on the domain, either exterior or with multiple cylindrical branches, which guarantee that any transition front has a global mean speed.

## A New Predictor of Diabetes from a Longitudinal Mathematical Model

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Diabetes, defined by high plasma glucose, is a progressive disease that requires prevention and early intervention for disease control. There is thus growing interest in finding early signs of the disease. Glucose that is elevated but not in the diabetic range indicates increased risk of diabetes. The gold-standard clinical test is the oral glucose tolerance test (OGTT), in which blood is sampled at several time points over two hours for glucose and insulin measurements. The current diagnostic criteria for diabetes, however, use glucose measurements only at  $t=0$  and 2 hours. In contrast, we fit a longitudinal mathematical model of diabetes progression (Ha et al. Endo. 2016) to all the glucose and insulin data in an OGTT. This method identifies two major metabolic parameters, insulin sensitivity and beta-cell function, which are predictive of diabetes risk. However, insulin measurements are often not available or of questionable quality. Without insulin, the model cannot identify sensitivity and function separately but only their product. This product is analogous to the disposition index (DI), a heritable marker often used in clinical trials to quantify diabetes risk. We tested the DI of our model on multiple prospective data sets to assess its ability to predict future diabetes vs. the current criteria. We found that our DI has higher sensitivity and specificity as measured by the area under the curve in receiver operating characteristic (ROC) analysis. This approach may also be applicable to other types of data, such as glucose self-monitoring data collected by patients, which are not accompanied by insulin.

## A DTI-based continuum mechanics computational model of glioma

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Glioblastoma is an aggressive form of brain cancer, with patients having an average life expectancy of 14 months using current treatment methods. Several mathematical models for glioma modeling are available in the literature, but they all struggle with the issue of including brain-tissue mechanics. Based on recent measurements of mechanical brain-tissue response, we will develop a new mechanical approach for the deformation of brain tissue as a result of an expanding glioma. As a proof-of-concept, I will discuss the one-dimensional version of the model and analyze deformations that are caused by a growing tumor.

## Computational modeling of the effects of mechanosensory feedback on swimming lamprey

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Lampreys are vertebrates with a relatively simple swimming mode used as a model for both neurophysiology and locomotion research. Swimming in lampreys is driven by a neural network called a central pattern generator (CPG) which is used to generate rhythmic contraction-inducing signals down the body. Mechanosensors (edge cells) detect changes in the body to adjust the signal and improve performance. While the effects have been studied for some time, the exact functional form of the resulting feedback from the edge cells to the CPG is not well understood. To examine the effects of different function forms of feedback, we present a computational swimming lamprey driven by a CPG modelled as a chain of coupled oscillators with curvature-based feedback used to close the physiological loop. Implications for steady swimming, maneuverability, and costs associated with locomotion will be considered and discussed.

## A next generation model for the spread of marine organisms between population patches

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Source-sink theory in ecology is useful in quantifying the effect of specific habitat patches on the dynamics of connected populations. In marine systems, populations on isolated habitat patches are connected by larval dispersal, with adult stages that then remain on a patch. Recently, next generation operators, popularized in epidemiology, have been used to calculate source-sink distributions in connected populations. In this talk, we present a stage structured model for a marine population, composed of several sessile stages which grow on a habitat patch, and a larval stage that can disperse between habitat patches. We calculate the next generation matrix for this model and demonstrate how we can use the next generation matrix to calculate the source-sink distribution of habitat patches. We then investigate the effect of different environmental variables on the source-sink distribution, and how the source-sink distribution can reveal interesting transient dynamics of the model.

## An extension to the Toxicant mediated Predator-prey model under Stoichiometric Constraints

Md Nazmul Hassan (presenter)<sup>a</sup> and Angela Peace<sup>b</sup>

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Studies in ecological stoichiometry highlight that grazer dynamics are affected by insufficient food nutrient content (low phosphorus (P)/carbon (C) ratio) as well as excess food nutrient content (high P:C). Contaminant stressors affect all levels of the biological hierarchy, from cells to organs to organisms to populations to entire ecosystems. Eco-toxicological modeling under the framework of ecological stoichiometry predicts the risk of bio-accumulation of a toxicant under stoichiometric constraints. Here, we developed and analyzed a LotkaVolterra type predator-prey model which explicitly tracks the environmental toxicant as well as the toxicant in the populations under stoichiometric constraints. Analytic, numerical, slow-fast steady state and bifurcation theory are employed to predict the risk of toxicant bio-accumulation under varying food conditions. In some cases, our model predicts higher individual toxicity on grazer (body burden) compared to the previous model which increases the effectiveness of risk assessment protocols.

## Waning and herd immunity

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Immunity within a population varies by age, and vaccine and disease history. Waning immunity (whether from vaccination or infection) can also affect population immunity distribution, affecting herd immunity. In this talk we will review new models of waning immunity within an immunity and age structured population. Immigration rates whereby immune systems are imported into populations are also studied.

## Multiple-scale analysis of a stoichiometric cyanobacteria model with phosphorus impulses

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Cyanobacterial blooms are becoming a global concern due to the increasing prevalence of eutrophication. The dependence of cyanobacteria dynamics on phosphorus and light inputs is modeled via stoichiometric approach. The dynamics occur in distinct phases that allow us to make use of multiple time-scale analysis to uncover the driving mechanisms of each phase. As a result, we are able to approximate the length of time a bloom persists after an impulse of phosphorus. This framework helps to establish the use of multi-scale methods in stoichiometric models, and provides deeper understanding of cyanobacteria dynamics.

## The microtubule-associated proteins tau and MAP7 direct organelle transport

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Organelles, proteins, and mRNA are transported along microtubules by plus-end directed kinesin and minus-end directed dynein motors. Microtubules are decorated by microtubule associated proteins (MAPs) that organize the cytoskeleton, regulate microtubule dynamics, and control the interaction between motor proteins and microtubules. By differentially regulating kinesin and dynein motors, MAPs direct trafficking towards the microtubule plus or minus end. We examined the role of two MAPs localized to neuronal axons, tau and MAP7, in directing transport.

Dysregulation of tau leads to a range of neurodegenerative diseases known as tauopathies including Alzheimer's disease (AD). Tau reduces the processivity of kinesin and dynein by acting as an obstacle on the microtubule, and single-molecule assays indicate that kinesin-1 is more strongly inhibited than kinesin-2 or dynein. To investigate the role of tau in regulating bidirectional transport, we isolated phagosomes driven by kinesin-1, kinesin-2, and dynein and reconstituted their motility along microtubules. We find that tau biases bidirectional motility towards the microtubule minus-end in a dose-dependent manner. Optical trapping measurements show that tau increases the magnitude and frequency of forces exerted by dynein through inhibiting opposing kinesin motors.

MAP7 (ensconsin, E-MAP-115) is a ubiquitous microtubule-associated protein that organizes the microtubule cytoskeleton in mitosis and neuronal branching. MAP7 also recruits kinesin-1 to microtubules. In contrast to tau, MAP7 induces a pronounced shift in motility towards the microtubule plus end – phagosomes move towards the plus end ~80% of the time and kinesin teams generate more force. To dissect MAP7-mediated regulation of kinesin-driven transport, we examined its effects on the motility and force generation of single and teams of full-length kinesin-1 motors. We find that MAP7 does not alter the force exerted by a single kinesin-1 motor, but instead increases its binding rate to the microtubule. In turn for ensembles of kinesin, a greater number of kinesin motors are simultaneously engaged and generating force to target organelles toward the microtubule plus end.

Thus, each MAP has specific effects on motor function. Through mediating the interaction between motors and the microtubule lattice, MAPs tune the balance of plus- and minus-end directed transport.

# Immune therapy for treating secondary bacterial infections during severe influenza infections

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In the course of influenza A virus (IAV) infections, a secondary bacterial infection mainly driven by *Streptococcus pneumoniae* (Sp) is a main causative agent for severe respiratory diseases provoking high rates of hospitalization and death tolls. Although abundant pro-inflammatory responses are reported in acute IAV infections, its role in facilitating bacterial colonization is debatable.

In this work, mice were infected with sublethal doses of IAV or Sp or co-infected with Sp seven days following IAV. The viral and bacterial burden, alveolar macrophage numbers and the concentrations of IFN-gamma, IL-6, TNF-alpha, MCP-1, IL-22, IFN-beta and GM-CSF in the respiratory tract were closely monitored.

Mathematical model selection procedures highlight IFN-gamma kinetics as a main candidate responsible to impair bacterial clearance promoting the bacterial burden and systemic dissemination observed 18 hours post-secondary infection with Sp during acute IAV infection. Moreover, we found a contribution but not conclusive of IL-6 to impaired bacterial clearance.

Ultimately, a continuous close cooperation of theory and experiments was developed to tailor windows of opportunity for immune therapeutic approaches to treat and prevent secondary bacterial infections during severe influenza infections. Murine experiments revealed the success and pitfalls of immune therapeutic approaches within IAV-Sp coinfection.

## Spreading of molecular mechanical perturbations on linear filaments

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Global changes in the state of spatially distributed systems can often be traced back to events resulting from local interactions. Whether the results of local interactions grow into global changes, however, depends (i) on the system geometry and (ii) the spatial spreading of the outcomes of local interactions. Here, we investigate how different spreading behaviors of local events determine their global impact in one-dimensional systems of different size. In particular, we combine *in vitro* experiments where groups of myosin motors propel actin filaments, single-molecule resolution simulations of these *in vitro* experiments, and an abstracted spin chain model. All three approaches lead to the same two conclusions. First, local events that become long-term stable only after they have spread to full system size have more impact in smaller systems. Second, local events that are relatively stable upon initial occurrence and then spread to full system size have more impact in larger systems. Our work provides highly specific predictions for future experiments that resolve actin-myosin-crosslinker interactions along actin filaments. Also, the conclusions from our work should generally apply to local-to-global spreading in finite, one-dimensional geometries. (Preprint: <https://www.biorxiv.org/content/10.1101/573261v1>)

## Homogenization of Transport Equations

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Almost all natural habitats exhibit spatial heterogeneities. Ecological processes are affected by heterogeneous resource distributions and species are required to adapt to changing environments. The method of homogenization has recently entered the area of ecology and helped to understand multiscale averaging in this context. Most spatial models are of the form of reaction-diffusion models. Here, we extend the existing methods to include transport equations.

Transport equations are spatial models for situations where speeds and turning rates of individuals have been measured. As more and more individual track data become available, transport equations gain in significance. We derive the homogenization of the  $n$ -dimensional transport equation, and, for the one-dimensional case, we consider jump discontinuities on habitat boundaries. In the limit of fast turning and fast speeds (parabolic scaling) our results match closely to known results for reaction-diffusion models. (Joint work with F. Lutscher).

## Targeting Heterogeneity: Yard-scale Treatments to Reduce Citywide *Aedes* Populations

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The spatial distributions of *Aedes* populations are well known to be extremely heterogeneous across small distances, with areas of high mosquito density often confined to only a few square meters. Despite this, insecticide applications for general mosquito control, and especially for the control of mosquito-borne disease, is applied uniformly across large areas of space, often on the scale of square kilometers, using ultra-low volume (ULV) spraying from vehicle-mounted sprayers. This indiscriminate application can have implications for numerous ecological and evolutionary processes, including the evolution of insecticide resistance and off-target mortality. Here, we examine the alternative of using small-scale precision treatments and their effects on the larger-scale mosquito population. Using a field experiment conducted in the summer of 2018, we first attempt to quantify the effect of yard-scale treatments on mosquito densities both inside the treated area and in surrounding untreated areas. Next, we use the results of this study to parameterize a model of yard-scale mosquito control in a neighborhood with a heterogeneously distributed mosquito population and compare its effects on the neighborhood wide population with traditional ULV sprays. Finally, we discuss implications of heterogeneity on the spread and control of mosquito-borne diseases.

## Analyzing the sleep patterns of shift workers using the mathematical model

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There is increasing interest in the possibility that shift workers have increased risk of excessive daytime sleepiness, insomnia and even cancer. While shift workers suffer from excessive daytime sleepiness and insomnia, the cause of daytime sleepiness and insomnia remains unclear. To identify such cause, we analyzed complicated sleep patterns of 23 nurses on a rotating shift schedule collected for 14 days from Samsung hospital. For this, we use an established neuronal population model of the sleep-wake cycle which includes mutual inhibition between wake-promoting and sleep-promoting neurons, as well as drive consisting of circadian rhythm and the homeostatic sleep pressure. This analysis leads to the development of a new index called Sufficient Sleep Percentage (SSP) which is the first index to predict daytime sleepiness and insomnia of shift workers from their sleep patterns. This shows how the mathematical model can be used to provide optimal sleepwake schedules to improve sleep qualities of shift workers.

# On the Traveling Waves for Degenerate Reaction-Diffusion Equation

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This talk is considered with the existence and stability of traveling wave solutions for a degenerate reaction-diffusion equation with time delay. We first show the existence of smooth- and sharp-type traveling wave solutions for the degenerate reaction-diffusion equation without delay. Then, as a small perturbation, we obtain the existence of the smooth non-critical traveling waves for the degenerate diffusion equation with small time delay. We also consider the regularity of the solutions to the time-delayed degenerate reaction-diffusion equation via compactness analysis. Finally, we prove that the smooth non-critical traveling wave is globally stable. This is a joint work with Professors C. Jin, M. Mei and J. Yin.

# Speed Selection for Traveling Waves of a Reaction-diffusion-advection Equation in a Cylinder

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Zhe Huang is the presenter.

In this talk, we concern with the linear or nonlinear selection mechanism for the minimal speed of traveling wave solutions to a reaction-diffusion-advection equation in a cylindrical domain with a Fisher-KPP type nonlinearity. By using the upper and/or lower solutions method, we establish the speed selection mechanism. Precisely, we obtain sufficient conditions for which a linear or nonlinear selection is realized when the model is prescribed with Neumann boundary conditions and Dirichlet boundary conditions respectively.

## Amplitude variation in glucose-insulin ultradian dynamics

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Glucose-insulin oscillations in the ultradian regime is generally believed to result from a feedback loop between pancreatic and hepatic secretory dynamics. These rhythms have been best observed clinically under a glucose stimulus, in the form of a constant or periodic infusion [Sturis *et al.*, J Clin Invest, 1991]. They have been seen to be gradually damped by increasing insulin resistance, ultimately leading to a lack of control of the oscillations [O'meara *et al.*, J Clin Invest, 1993].

In this contribution, we study this phenomenon in a quantitative way using a reduced polynomial model of glucose-insulin ultradian dynamics based on the system introduced in [Li *et al.*, J Theor Biol, 2006], which includes delays in pancreatic and hepatic actions. The location of Hopf bifurcation points in the space of delays is characterised by studying a specific linear combination of Chebyshev polynomials. A periodic perturbative scheme is devised to study the nonlinear relationship between insulin-dependent glucose uptake, hepatic glycogenesis, pancreatic insulin secretion and inherent delays to the amplitude and frequency of the oscillatory regime. In particular, it is shown that these latter remain almost constant within a band along the Hopf threshold curve. Applications to potential glycemic control strategies will be explored.

## Using Trap Data to Study Aedes aegypti Population in South Florida

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Aedes aegypti is the primary mosquito species responsible to the spread of many vector-borne diseases, such as dengue fever, chikungunya, Zika virus, and yellow fever viruses. In this talk, I will present the models we use to study the Aedes aegypti population dynamics in South Florida, the impacts of vector control on the outbreaks of vector-borne diseases, and the methods we apply to fit the model parameters to trap data.

## Parameters Influencing Brain Folding Pattern Development

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The folding patterns of the human brain vary greatly in their shape, size, and extent across individuals in the human brain. Certain diseases, such as bipolar disorder and schizophrenia, have been linked with specific, yet subtle, folding pattern variations in certain folds of the brain, although the evidence is not conclusive. The complexity of brain folding patterns make it extremely challenging to study brain diseases since there is such variability in the folding patterns across healthy individuals. Interestingly, there is also no consensus in the biology as to the how, why, and where of fold formation.

In this presentation, I will discuss some of the biological hypotheses of folding pattern formation and present some mathematical models that my research group is developing to investigate these theories, including biochemical and biomechanical models. Factors that influence the size and shape of folding pattern formation, such as domain size and chemical genetic control, will be presented. The results of these models can be utilized to explain certain observations in human diseases of cortical folding, such as polymicrogyria and Norman Robert's Syndrome. Our models illustrate the importance of how mathematical modeling can help investigate an area of neuroscience where it is difficult to perform human experiments.

# The Optimal control of HPV Infection and Cervical Cancer with HPV vaccine

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## Abstract

Cervical cancer is by far the most common HPV-related disease. Nearly all cases of cervical cancer can be attributable to HPV infection. In this paper, we develop a model for the transmission dynamics of Human Papilloma Virus infection leading to cervical cancer. There are three types of vaccines available and we investigate the best vaccine for an ideal control: a bivalent vaccine which gives longer protection and targets two types of Human Papilloma Virus 16 and 18. In the case of a single vaccine, the basic reproduction number  $R_0$  and the disease-free equilibrium for the given model are calculated in terms of related parameters. Also, the stability of the disease-free equilibrium in terms of  $R_0$  is established which is locally asymptotically stable when  $R_0 < 1$  and unstable when  $R_0 > 1$  and global stability occurs when  $R_0 \leq 1$ . In a sensitivity analysis we determined that the model is highly sensitive to the parameters  $\beta$  and  $\epsilon$ . Moreover assuming infection predominance, the optimal control strategy is utilized to construct vaccination methodologies for the given model. The result of those techniques on the infected population and therefore the accrued cost is assessed. Furthermore, the optimal control strategy is also used for multiple vaccinations with cross-protection and without cross-protection.

## Signaling in the presence of cellular substructures

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The cytosol of mammalian cells is a heterogeneous, crowded environment, packed with organelles and proteins. In this work we reconstruct the 3D geometry of cytosolic organelles from whole-cell soft X-ray tomograms, and investigate how the presence of organelle barriers can influence the propagation of a diffusive signal from the cell membrane to nucleus. We demonstrate a simple chemical mechanism that provides robustness, with respect to spatial heterogeneity within the cytosol, in the time required for signals to reach the nuclear membrane.

## Optimising an anti-adhesion treatment for a *P. aeruginosa* bacterial infection

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The ability of bacteria to become resistant to previously successful antibiotic treatments is an urgent and increasing worldwide problem. Solutions can be sought via a number of methods including, for example, identifying novel antibiotics, re-engineering existing antibiotics or developing alternative treatment methods. The nonlinear interactions involved in infection and treatment render it difficult to predict the success of any of these approaches without the use of computational tools in addition to more traditional experimental work.

We use mathematical modelling to aid in the development of anti-virulence treatments that, unlike conventional antibiotics that directly target a bacterium's survival, may instead attenuate bacteria and prevent them from being able to cause infection. Many of these anti-virulence treatments, however, are only partially successful when tested in infection models. We apply our interdisciplinary approach specifically to MAM7-based inhibitory beads, used to prevent *P. aeruginosa* from adhering to host cells (a key early stage in infection). By carefully combining ordinary differential equation models with experimental data, we are able to produce reliable mathematical models of different treatment scenarios.

Computational optimisation procedures are applied to make experimentally-testable predictions regarding combinations of treatments that should minimise the bacterial load. In particular, we consider an antibiotic-resistant infection and predict that MAM7-based inhibitory beads can be successful in clearing an antibiotic resistant infection when combined in an appropriate way with antibiotics and/or debridement.

## Quantifying immunosuppression by type 1 regulatory T cells in simultaneous autoimmune disorders

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Type 1 regulatory T cells are a class of immunosuppressive CD4<sup>+</sup> cells that undergo massive proliferation *in vivo* upon administration of nanoparticles coated with peptide-major histocompatibility complex. Treatment with mitochondrial peptide-derived nanoparticles has been shown to blunt autoimmune responses against either the liver or the brain in mice. In the case of simultaneous autoimmunity in both of these tissues, however, these nanoparticles preferentially treat the liver, leaving the brain untreated. In contrast, oligodendrocyte-derived nanoparticles can treat the brain but not the liver in mice with both disorders. To investigate this, we developed a mathematical population model of regulatory T cell allocation in mice with simultaneous liver and brain autoimmunity. We use tools and techniques in nonlinear dynamics to perform time series simulations and bifurcation analyses, and study the effects of varying physiological parameter values on the resulting cellular dynamics. The model allows us to examine the effects of tissue size and of regulatory cell recruitment, retention, and efficacy, on the kinetics of T cell allocation and immunosuppression. Our results suggest that a transient delay in regulatory T-cell recruitment to the brain during simultaneous autoimmunity forms the physiological basis of the observed phenomena of mitochondrial peptide-derived nanoparticle therapy, and that Tr1 cell retention in a specific tissue (rather than tissue size) is a key determinant of treatment outcomes. It also shows that different peptide expression levels and Tr1 cell specificities can reverse these outcomes, as seen with oligodendrocyte-based nanoparticle therapy. This study thus provides insights into how nanoparticle-dependent expansion of type 1 regulatory T cells exerts immunosuppression.

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**Title:** Modeling of preclinical studies of breast cancer response to evaluate therapeutic regimens

**Abstract:** Preclinical, experimental studies of breast cancer offer a focused view of tumor cell response to various chemotherapies, allowing for assessments of the effectiveness and interactions of specific therapeutic protocols in a controlled setting. However, it is often difficult to draw conclusions across experiments and experimental scales about the mechanisms of action of therapies or optimal combination regimens with these data alone. Here we present a mathematical model at the tissue scale describing the temporal relationship between vasculature, hypoxia, necrosis, and tumor growth to predict changes in immune infiltration for a preclinical model of breast cancer undergoing targeted therapy. This *in vivo* model, consisting of five ordinary differential equations, is calibrated with data across several experiments: 1) tumor volume is assessed *via* caliper measurements, 2) vasculature *via* magnetic resonance imaging 3) hypoxia *via* positron emission tomography, and 4) necrosis *via* histology. Uncertainty analysis is used to verify plausible overlap between the model's simulations and the experimental data when considering calibration error. Sensitivity analysis is also applied to identify important parameters to narrow the scope of experimental investigation and propose testable hypotheses for follow-up studies. We also present future directions for this modeling effort including an expansion to multiple scales by merging the *in vivo* scale model with an *in vitro* scale model describing cellular responses to anti-cancer therapies. The *in vitro* scale model was built to explicitly include the effects of combination targeted and cytotoxic therapies and evaluate potential synergies between drugs as measured by time-resolved microscopy of *in vitro* breast cancer cells. Evaluating the dosing of combination therapy *in vitro* provides the opportunity to quantify the cellular effects of treatment, which is not feasible to collect in an *in vivo* setting under a multitude of conditions (e.g., order and timing of drugs). Therefore, our aim is to generate experimentally testable predictions for optimizing combination therapy in preclinical tumor models of breast cancer with our multiscale model. We posit that an integrated mathematical-experimental approach bridging *in vitro* and *in vivo* experimental data can elucidate the optimal strategies for combination therapy. This is an important step for future clinical translation as we aim to provide guidance on the timing of combination therapies to maximize patient response.

Combining metabolic modeling and microbiome analyses to uncover novel mechanisms of metabolism-linked *Clostridium difficile* virulence regulation

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*Clostridoides (Clostridium) difficile* is a Gram-positive, sporulating anaerobic bacterium that has become the leading cause of hospital-acquired infection. Incidence of hypervirulent and recurrent infections have also significantly increased over the last decade. Exposure to antibiotics sensitizes hosts to colonization by *C. difficile* through disruption of the healthy gut microbiota. Previous studies have strongly supported that the microbiota may prevent *C. difficile* colonization through competition for growth nutrients, however it has also been demonstrated that the metabolic profile of the intestines drives *C. difficile* virulence activation following infection. Previously, this complex interplay between metabolism between the microbiome and pathogen has been difficult to characterize mechanisms by which groups of bacterial species or functionality determine resistance to infection or contribute to the onset of disease. Recently, integrative, systems biology approaches have modeled bacterial pathogen metabolism at the genome-scale and revealed novel metabolic determinants of virulence regulation. These techniques may be applied to *C. difficile*, in concert with large-scale microbiome analyses, to elucidate novel metabolic control mechanisms of *C. difficile* virulence that are influenced by the behavior of the microbiota. In order to capture novel metabolic regulation patterns of virulence, I have generated a curated metabolic reconstruction *C. difficile* str. 630 to match known growth substrate utilization patterns during infection. I have also developed novel transcriptomic integration algorithm for metabolic networks that is suited for in vivo transcriptomic analysis, and preliminary data from these efforts strongly supports context-specific metabolic behaviors of *C. difficile*. This includes differential patterns of access to certain nutrients with potential links to virulence factor expression. By formalizing the relationship between *C. difficile* virulence and metabolism in our metabolic reconstruction, I can begin to explore mechanistic relationships between microbial metabolism in the gastrointestinal tract and *C. difficile*-associated disease. To achieve this understanding, I have created a robust computational framework in which to integrate omic data collected from during *in vivo* infection, in order to predict the contribute of individual metabolite concentrations on *C. difficile* virulence activation. Ultimately, by identifying metabolic properties of resistant communities or additional metabolic signals which dampen *C. difficile* virulence expression, we may augment downstream development of targeted probiotic therapies and improve antibiotic stewardship.

## Viro-immunotherapy for Glioblastomas: In Silico Optimisation of Therapy Delivery

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Glioblastoma is an aggressive brain cancer which is incurable due to its resistance to conventional chemotherapy and radiotherapy. Recently, viro-immunotherapeutic agents have been considered as a way of by-passing the resistance of glioblastoma cells to conventional therapies. However, as expected, this type of therapy comes with its own challenges. The brain is built with a protective mechanism unlike other areas of the body and while this therapy is able to enter the brain seamlessly, it is rapidly cleared once it arrives at the tumour site. Overcoming and then balancing the clearance-delivery aspect of this novel therapy is challenging and expensive in the experimental and clinical setting. Extending the cellular automaton platform PhysiCell developed by Paul Macklin, we have constructed a model that encapsulates the interplay of viro-immunotherapy with a growing glioblastoma. Balancing therapy delivery with toxicity results in some interesting optimal injection profiles. The extensions to the current PhysiCell platform form an educational and insightful tool that may be translated into other areas of medical modelling.

# Global Solvability and Stabilization to a Cancer Invasion Model with Remodelling of ECM

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## Abstract

We consider the Chaplain-Lolas's model of cancer invasion with tissue remodelling

$$\begin{cases} u_t = \Delta u - \chi \nabla \cdot (u \nabla v) - \xi \nabla \cdot (u \nabla \omega) + \mu u(1-u) + \beta uv, \\ v_t = D \Delta v + u - uv, \\ \omega_t = -\delta v \omega + \eta \omega(1-\omega). \end{cases}$$

We study this problem in a bounded domain  $\Omega \subset \mathbb{R}^N$  ( $N = 2, 3$ ) with zero-flux boundary conditions. We first establish the global existence and uniform boundedness of solutions. Subsequently, we also consider the large time behavior of solutions, and show that the global classical solution  $(u, v, \omega)$  strongly converges to the semi-trivial steady state  $(1 + \frac{\beta}{\mu}, 1, 0)$  in the large time limit if  $\delta > \eta$ ; and strongly converges to  $(1 + \frac{\beta}{\mu}, 1, 1 - \frac{\delta}{\eta})$  if  $\delta < \eta$ . Unfortunately, for the case  $\delta = \eta$ , we only prove that  $(v, \omega) \rightarrow (1, 0)$ , and it is hard to obtain the large time limit of  $u$  due to lack of uniform boundedness of  $\|\nabla \omega\|_{L^2}$ . It is worth noting that the large time behavior of solutions for the chemotaxis-haptotaxis model with tissue remodelling has never been touched before, this paper is the first attempt.

# Persistence and global stability for biochemical reaction-diffusion systems

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**Abstract:** The investigation of the dynamics of solutions of nonlinear reaction-diffusion PDE systems generated by biochemical networks is a great challenge; in general, even the existence of classical solutions is difficult to establish. On the other hand, these kinds of problems appear very often in biological applications, e.g., when trying to understand the role of spatial inhomogeneities in living cells. We discuss the persistence and global stability properties of special classes of such systems, under additional assumptions such as: low number of species, complex balance or weak reversibility.

An integrated approach to calibrate and validate mathematical models of therapy-induced resistance from in vitro drug response data in cancer

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The development of resistance to chemotherapy is a major cause of treatment failure in cancer. Intratumoral heterogeneity and phenotypic plasticity are known to play significant roles in drug resistance. The contribution of therapy-induced resistance is an area of increased interest as it has direct consequences for the optimization of treatment protocols. To elucidate the mechanistic roles of heterogeneity and plasticity in chemotherapy resistance, therapeutic response should be evaluated using both phenotypic characterization and bulk population dynamics. However, integrating multiple data types into a comprehensive mathematical modeling framework has remained a challenge in the field. In this work, we develop an integrated mathematical-experimental approach to calibrate and validate a model of drug-induced resistance. In order to "see under the hood" and understand the molecular underpinnings of drug response dynamics, we utilize recent advances in single cell RNA sequencing and single cell lineage tracing to better understand the molecular underpinnings of the drug response at the individual cell level. Using lineage tracing to track clonal dynamics, we are able to identify the fate of resistant and sensitive subpopulations and characterize the gene expression states associated with chemotherapy resistance. Using principle component analysis, we can classify cells from downstream post-treatment time points into sensitive and resistant states to obtain estimates of the phenotypic composition of the cancer cell population over time. The phenotypic composition dynamics are combined with longitudinal drug response dynamic data and calibrated to a mathematical model of drug-induced resistance. We validate the model by comparing model predictions of repeat treatments at different time intervals to experimental observations of subsequent treatments. This framework is the first work to our knowledge that combines time-resolved single cell RNA sequencing and lineage tracing with mathematical modeling to reveal the dynamics of drug-induced resistance.

## Characterizing the landscape of epithelial-mesenchymal plasticity in cancer metastasis

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Epithelial-mesenchymal plasticity (EMP) underlies many aspects of cancer metastasis such as collective cell migration, tumor-initiation potential and resistance to multiple therapies. Recent in vitro, in vivo, and clinical studies have identified that cells maintaining one or more hybrid epithelial/mesenchymal (E/M) phenotypes are likely to be more aggressive than cells in extremely epithelial or extremely mesenchymal ones. However, how cells maintain these hybrid E/M phenotypes remain elusive. Here, we simulated multiple regulatory networks implicated in EMP to identify their impact on stabilizing hybrid E/M phenotypes, using a combination of mathematical and statistical modeling strategies. We have identified novel 'phenotypic stability factors' (PSFs) that can stabilize these hybrid E/M phenotypes, and present relevant experimental data and clinical correlation of PSFs with patient survival, thus suggesting how these PSFs may play a key role in accelerating cancer metastasis.

## Steady State Parametrizations for Biochemical Reaction Systems

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Significant work has been conducted in recent years on establishing recurring motifs in biochemical interaction networks, such as signal transduction cascades and gene regulatory networks, which are predictive of experimentally observed behaviors. Work in this area is notably challenging due to the significant number of species involved in typical biochemical reaction pathways and the unknown values of the rate parameters. In this talk, we focus on recent results on parametrizing the steady state sets of large biochemical reaction systems with mass action kinetics. We also present computational work toward the goal of integrating the theory with practice. Applications include the EnvZ-OmpR osmoregularity pathway and the Shuttled WNT signaling pathway.

## A stochastic model of autocatalytic reaction networks

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Autocatalytic reaction networks which display cooperative behavior have been proposed as the basis for origins of molecular ecosystems and origins of life. We define a continuous-time Markov chain model and show that under the appropriate scaling, it converges to a system of ODEs in a strong sense. Furthermore, we give a characterization for the stationary distribution of the Markov chain.

## How 4D Printing Helps Students Explore Self-Assembly, Geometry, Topology and Combinatorics

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Many beautiful biological structures are self-assembled, yet there is a common misconception that to generate such beautiful patterns cells must do enthalpic work. Instead, self-assembly of many proteinaceous complexes such as viral capsids are produced by entropy-driven processes. How is it that random motion yields these beautiful biological structures? Since static models do not let students actually generate structures, it is important to have them interact with dynamic mathematical manipulatives. In 2007, Olson et al. (Olson, Arthur J., Yunfeng HE Hu, and Ehud Keinan. (2007). "Chemical mimicry of viral capsid self-assembly." Proceedings of the National Academy of Sciences 104, no. 52: 20731-20736.) produced self-assembling dodecahedra models of viral capsids through 4D printing and subsequently demonstrated how helpful they were in biology education (Hst, Gunnar E., Caroline Larsson, Arthur Olson, and Lena AE Tibell. (2013). "Student learning about biomolecular self-assembly using two different external representations." CBELife Sciences Education 12 (3): 471-482.). My students and I have been able to reproduce their work and build three different self-assembling icosahedral models of viral capsids. The areas of mathematics that we use beyond Euclidean geometry are two planar projections (Durer nets for origami self-folding models and Schlegel diagrams for topological relationships between subunits), combinatorial explosions of folding and assembly pathways and configurations, Caspar-Klug tiling theory of Goldberg polyhedra, quasicrystal tilings, Hamiltonian paths of RNA assisted assemblies, Schläfli-Coxeter-Poincaré's extension of Euler's "gem" on vertices, edges, and faces to include cells of packed polyhedra, and graph theory applied to rigidity and flexibility in tensegrity structures.

## A Mathematical Model for Enzyme Clustering in Glucose Metabolism

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Sequential enzymes in glucose metabolism regulate glycolysis and gluconeogenesis in living cells. It has long been hypothesized that these enzymes form multienzyme complexes and control glucose flux. We have recently demonstrated that the rate-limiting enzymes in the cytoplasm are organized as a multienzyme complex, the glucosome. Quantitative high-content imaging data support a hypothesis that the glucosome clusters regulate the direction of glucose flux between energy metabolism and building block biosynthesis. However, direct measurement of their functional contributions to cellular metabolism at subcellular levels has remained to be challenging. To support this finding, we develop a mathematical model, in which the association of the rate-limiting enzymes into multienzyme complexes is included as an essential element. We then demonstrate that our mathematical model provides a quantitative principle to simulate the direction of glucose flux at both subcellular and population levels in human cancer cells.

## Population Dynamics of Honeybees: Effects of Parasites and Nutrition

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Honeybees are important pollinators worldwide and pollinate about one-third of the food we consume. The incidence of honeybee colony collapsing has been increased under increasing stress due to global warming, pesticides, mites, viruses and nutrition status. In this talk we would start with experimental data and the related analysis from Dr. Gloria Hoffman. The data suggests that low initial bee populations lead to collapse in September while mites and viruses can lead to collapse in December. Feeding bee colonies also has a mixed effect, where it increases both bee and mite populations. Based on the data, we provide our modeling approach by using nonlinear distributed delay differential equations. Our proposed model includes both age structure of honeybees and mites. Some of our interesting finding from our proposed model is including but not limit to: (1)Initial populations are important for the survival of colony; (2)Mite can destabilize honeybee populations and potentially lead to the colony collapsing; and (3) delay term can also destabilize the honeybee-mite interaction dynamics. Our ongoing work is validating our proposed model with data.

## A Single-Cell Resolution Map of EMT and Drug Resistance States in NSCLC

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Defining the spectrum of EMT and MET cancer states in clinical samples is critical for understanding and clinically targeting EMT processes, including drug resistance. Toward this goal, we first dynamically capture and characterize intermediate EMT and MET states through TGF time-course treatment and withdrawal in lung cancer cells. Through mass cytometry time-course analysis we resolve previously unrealized EMT and MET states at the single-cell level, and demonstrate significant differences between EMT and MET trajectories using a novel computational tool (TRACER) for reconstructing trajectories between cell states. We then construct a lung cancer reference map of the identified EMT and MET states referred to as the EMT-MET STAtic MaP (STAMP). Using a neural net algorithm we project lung cancer clinical samples onto the EMT-MET STAMP to characterize their phenotypic profile with single-cell resolution in terms of our in vitro EMT-MET analysis. Finally, we extend our mass cytometry time-course analysis to lung cancer cells that underwent various drug treatments and withdrawal to augment our EMT-MET STAMP with drug resistance phenotypic traits. These data can be used to evaluate EMT-related drug resistant cell states that arise before, during and after the course of treatment in different lung cancer patient therapy time-points. In summary, we provide a framework that can be extended to phenotypically characterize clinical samples in the context of in vitro studies showing differential EMT-MET traits related to drug sensitivity. This framework provides a phenotypic foundation for evaluating – at a personalized level – disease status and response to treatment in lung cancer patients, and has broader applicability to understanding normal and pathological processes.

## Modeling of “replicator - genetic parasites” dynamics and coexistence

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Immunotherapy has a predator-like quality. It aims to alert, facilitate, and supplement the patient’s own immune systems to identify, seek out and kill cancer cells. As immunotherapies advance in sophistication and in combination with other therapies, appropriate conceptual frameworks and models will be necessary for improving the drug selection and dosing regimens. While descriptive models of tumor-immune interactions can provide some insights, we aim for conceptual and mathematical models for directing a more thorough and rigorous understanding of underlying mechanisms.

Tumor-immune interactions are frequently described and modeled as predator-prey type systems. However, such systems often exhibit oscillatory dynamics between predator and prey population sizes. While commonly seen in nature, such dynamics are not typically observed in cancer. Here we first provide an overview of key interactions between cancer and immune cells. We then provide several mechanistic explanations for the stabilizing and destabilizing factors that may determine oscillatory dynamics (or lack thereof) in cancer-immune interactions. These include possibilities for safety in numbers, resource supply, time delays and interference competition, among others. From a modelling perspective, the cancer cells and killer T-cells (a key component of the immune system) may best be seen as intra-guild predation and/or a system with intense interference competition. Furthermore, we can add the resources for which both populations compete, as well the other immune cells that modulate T-cell dynamics. In doing so we see that 1) the immune system is not a classical predator-prey system, 2) there are several feedbacks that may make dynamics more asymptotic rather than oscillatory, 3) the outcomes may include alternate stable states in which the immune system drives the cancer cells to extinction, or the cancer cells achieve numerical predominance, 4) the interaction structure of the immune system may be a whole organism adaptation to prevent oscillatory dynamics.

## Control of inward solidification in Cryobiology

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For many years, mathematical models that predict a cell's response to encroaching ice has played an important role in developing cryopreservation protocols. It is clear that information about the cellular state as a function of cooling rate can improve the design of cryopreservation protocols and explain reasons for cell damage during freezing. However, previous work has ignored the interaction between the important solutes, the effects on the state of the cell being frozen and encroaching ice fronts. In this talk, I will survey our work on this problem and examine the cryobiologically relevant setting of a spherically-symmetric model of a biological cell separated by a ternary fluid mixture from an encroaching solid–liquid interface and will illustrate our work on a simplified 1-D problem. In particular I will demonstrate how the thermal and chemical states inside the cell are influenced and can potentially be controlled by altering cooling protocols at the external boundary.

## Models for cell shape changes and cell motility: from one cell to many

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Cell shape and motility is determined by the actin cytoskeleton, a dynamic structural component of eukaryotic cells. Regulating the growth, distribution, and myosin-driven contraction of actin are proteins in the Rho GTPase family, known to form intracellular patterns of their own. In this talk I will address several questions: (1) How do GTPase patterns arise spontaneously inside a cell? (2) How does feedback between filamentous actin (F-actin) and GTPases lead to waves of activity?, and (3) How do properties of single cells scale up to cell populations and multicellular tissues given cell-cell interactions (adhesive, mechanical) between cells?

I will survey mathematical models including reaction-diffusion systems to model GTPase spatiotemporal dynamics, in models at various levels of detail. I will discuss examples of feedback (from mechanical tension, from F-actin) giving rise to Hopf bifurcations that accompany oscillatory behaviour and waves of activity in single and collective cell systems.

## Local and Global Regulation of GnRH Secretion: A Potential Neuroendocrine Mechanism for Pulsatile Release

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Pulsatile release of gonadotropin-releasing hormone (GnRH) from hypothalamic GnRH neurons is essential for reproductive health. Using different GnRH "cell-lines", previous studies have shown that these neurons (i) exhibit two modes of burst firing in their membrane potential in the time scale of seconds; (ii) they exhibit cytosolic calcium oscillations in the time scale of minutes; (iii) a subset of them express the GnRH receptor, a G-protein coupled receptor (GPCR), that allows for autocrine regulation; (iv) they respond to GnRH stimulation in a dose-dependent manner; and (v) they respond to stimulation to kisspeptin through a GPCR called GPR54. We recently developed a mathematical model of a single GnRH neuron that integrates all these components, occurring at different time scales, to explore how they interact collectively and produce pulsatile release in the time scale of hours. The model revealed that electrical activity, autocrine feedback and kisspeptin stimulation must act in synergy to produce such pulsatility. It also showed that kisspeptin acts as a global signal while autocrine feedback acts as a local signal to drive GnRH release, with approximately 7-1 locking between them, and that electrical activity controls baseline release as well as rare release events. Using pulse triggered average, we showed that this electrical activity was significantly reduced during a GnRH pulse, an unexpected outcome. In this talk, we will give an overview of these results and their implications.

### Reference

J Lehnert and A Khadra (2019). How pulsatile kisspeptin stimulation and GnRH autocrine feedback can drive GnRH secretion: A modeling investigation. *Endocrinology*, en.2018-00947, in press. <https://doi.org/10.1210/en.2018-00947>

# From LQ formalism to Mechanistic Models based Optimal Dosing in Radiotherapy

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## Abstract

Radiotherapy is an effective tool in the treatment of cancerous tumors. Dosage strategies currently employed vary from a large single dose or a few large doses (hypofractionation) to many smaller doses (hyperfractionation). Theoretical justification for these have traditionally been derived from a time-dose relationship widely used in radiotherapy, the Linear Quadratic (LQ) model. Different mechanistic models for the action of radiation on DNA leading to cell death have been proposed in the literature. In this talk we present a formulation of the optimal dosing problem using these mechanistic radiobiological models and present dosing schedules based on this approach. We compare the results with those obtained using the LQ model.

## Survival Dynamical Systems for the Population-level Analysis of Epidemics

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Motivated by the classical Susceptible-Infected-Recovered (SIR) epidemic models proposed by Kermack and Mckendrick, we consider a class of stochastic compartmental dynamical systems with a notion of partial ordering among the compartments. We call such systems uni-directional Mass Transfer Models (MTMs). We show that there is a natural way of interpreting a uni-directional MTM as a Survival Dynamical System (SDS) that is described in terms of survival functions instead of population counts. This SDS interpretation allows us to employ tools from survival analysis to address various issues with data collection and statistical inference of unidirectional MTMs. In particular, we propose and numerically validate a statistical inference procedure based on SDS-likelihoods. We use the SIR model as a running example to illustrate the ideas.

# **Mechanistic model for E7046, a PGE<sub>2</sub> Receptor Type 4 Antagonist for Cancer Immunotherapy.**

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Synthesis of Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) is one of the mechanisms by which tumours inhibit immune response. E7046 blocks this mechanism by inhibiting PGE<sub>2</sub> receptor type 4 (EP4). We developed a new mechanistic and quantitative model integrating new experimental data on immune system response to pre-clinical syngeneic CT-26 tumors and enhancement of this response by E7046. The data used for modeling included tumor infiltration by CD8 T-cells and monocytes, blood levels of CD8 T-cells, Treg, mMDSC, gMDSC cells, PGE<sub>2</sub> concentrations in blood and tumor, and the pharmacokinetics of E7046 in mice. Data were integrated with an ordinary differential equation model of 56 variables describing dynamics of molecular species and cell types in 11 compartments. The 138 parameters involved in 88 rate laws were established by literature meta-analysis and fitting to experimental data. Verification of model performance showed that it adequately predicted the TGI of CT-26 by E7046 in mice, as well as tumor and blood profiles of PGE2 and various cell populations. Three system parameters were identified as predictors of TGI by E7046: tumor CD8 T-cell infiltration, PGE2 levels, and tumor growth rate. Following calibration to CT-26 tumor values, these 3 markers allowed for successful prediction of TGI of 3 other syngeneic tumors in mice. The model also allowed exploration of TGI resulting from different doses of E7046 and its combination with a generic anti-PD1 checkpoint inhibitor.

## Systems model reveals the sources of the inter- and intraspecies variability in drug efficacy

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Circadian ( 24 h) clock synchronizes daily rhythms of physiology with day-night cycle. Failure of synchrony can lead to crucial physiological problems including cancer. Synchrony can be restored via phase adjustment of the circadian clock pharmacologically. However, the pharmacological intervention of circadian clock has been mainly investigated using nocturnal species (e.g. mice) although humans are diurnal. Here, using diurnal monkeys, we examine the effect of a daily (circadian) clock-modulator drug and find the high variability in its effect between diurnal monkeys and nocturnal mice. To identify the source of the interspecies variability, we used the systems pharmacology model, which accurately simulates the intracellular action of the drug and thus its effect in the circadian clock. This revealed that the interspecies variability in the drug effect is due to the different sensitivity of nocturnal and diurnal animals to environment light, the natural clock-modulator. Furthermore, via a combination of the model simulation and experiment, we found the molecular biomarker to predict the drug effect, which explains the high interindividual variability in the drug response. Based on these findings, we developed a model-based precision medicine strategy to treat circadian disruption. Our works show how the mathematical model can be used to reveal an unrecognized biological variable in drug efficacy translation between nocturnal and diurnal animals and enable precision medicine.

## Mathematical Model Driven Personalized Adaptive Therapy

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Despite the impressive responses of to targeted therapies, most metastatic melanoma (skin cancer) patients ultimately fail therapy. A major drive of treatment failure is intratumor heterogeneity. Adaptive therapy is an evolution-based strategy that exploits heterogeneity via the cost of resistance. For resistant cells, benefits exceed costs during therapy, however, in the absence of therapy, sensitive cells are fitter due to the cost of resistance. Therefore treatment holidays allow sensitive cells to outcompete their resistant counterparts, potentially extending response times whilst reducing treatment time. To predict precise timing of targeted therapy withdrawal and re-challenge, we developed a two-compartment ordinary differential equation model that describes the competition between sensitive and resistant cells and allows for transition between these states. We first tested mathematical-model-driven adaptive therapy on melanoma mouse models by predicting individual mouse specific adaptive treatment schedules, based on real-time model calibration of individual mouse tumor volume changes over time. The mouse-specific adaptive schedules were far more effective than continuous treatment, showing a reduction in burden of  $\sim 50\%$ . Surprisingly, the resulting treatment on-off schedules were quite diverse across the animals. Next, we considered metastatic melanoma patient data. Here, the patients were already treated with continuous therapy and their treatment responses were monitored by a tumor burden biomarker, Lactic Acid Dehydrogenase (LDH). We estimated model parameters from patient LDH resulting in a suite of parameter sets that fit the data equally well, defining a virtual cohort of patients. Using the cohort, we predicted responses to adaptive therapy that might delay tumor progression up to several months if the patients were treated with adaptive therapy instead of continuous therapy.

Stability and mixing times for stochastically modeled weakly reversible reaction networks with a single linkage class.

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Boundedness and persistence of the mass-action deterministic dynamics associated to weakly reversible reaction networks with a single linkage class have been studied a decade ago and it has been shown that for each trajectory  $x(t) \in \mathbb{R}_{\geq 0}^d$ , the expression  $\sum_{i=1}^d |\ln(x_i(t))|$  is uniformly bounded in time (Anderson 2011). Thus it is conjectured that the stochastically modeled analogs of these systems should all admit stationary distributions. In this talk we provide the main idea of the proof of this conjecture under the following additional assumptions: (i) the system is binary and (ii) for each species, there is a complex that consists solely of that species. To show this result, a new proof technique is developed in which we study the recurrence properties of the n-step embedded discrete time Markov chain. We will also talk about Poincare inequality of stochastic processes pertaining to our ongoing work for estimating the mixing time of the proposed model.

## Accurate simplification of multiscale deterministic and stochastic systems

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In biological systems, many species interact with multiple timescales. Because analysis and simulations of such multi-scale systems are challenging, various strategies to simplify the system have been developed. In this talk, I will describe a way to simplify deterministic and stochastic systems by projecting them to lower dimensional slow-manifold. I will also illustrate how we used such approach for 1) accurate prediction of drug clearance in human liver and 2) identification of molecular mechanisms underlying robust circadian rhythms against molecular noise.

## Mathematical model of tumor growth and anti-invasion strategies

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\* Presenter

In this talk, I will present some recent mathematical models of cancer growth and development which focus on designing anti-cancer strategies. We investigate the role of microenvironment in regulation of cellular dispersion and tumor growth. The results of the models will be compared with experimental data and some new directions of how to develop the new, innovative strategies of anti-invasion of tumor cells will be discussed.

## Evolutionary dynamics of non-Hodgkin's lymphoma CAR T cell therapy

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Non-Hodgkin Lymphoma (NHL) is the most common hematologic malignancy in the United States. Despite a possible cure, with front-line chemotherapy, there exist patients that do not respond or relapse and develop refractory disease. These patients have a median overall survival of less than seven months. Chimeric antigen receptor (CAR) T-cell therapy for refractory NHL relies on expansion of engineered T-cells that specifically target tumor cells expressing CD19. Here we combine mathematical modeling with statistical data-analysis based on recent results of clinical studies of CAR T-cell dynamics in individual patients. We use statistical and mathematical modeling to elucidate the key mechanisms that drive evolutionary dynamics of anti-CD19 CAR T-cell therapy. To this end, we integrate patient specific tumor burden profiles and CAR T cell population dynamics into our model. By incorporating the return of the patients' wildtype T-cells as a proxy for cytokine profiles, we find that the success of therapy depends on the interaction between wildtype and CAR T cells, as well as on specific properties of the heterogeneous CAR T-cell population. Relative abundances of juvenile and effector T cells are key factors that drive the duration of treatment response, and the tumor-killing rate of this CD19-specific immunotherapy. Our modeling framework elucidates disease and treatment specific eco-evolutionary dynamical properties, but can also quantify genetically engineered T-cell population properties related to neurological toxicity and long-term homeostatic mechanisms that determine patient survival. Finally, we investigate the impact of additional doses and identify key periods where this dose is beneficial to the patient.

## Multiscale Mathematical and Computational Models capturing *Mycobacterium tuberculosis* inhibition of Immunity during Tuberculosis infection

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*Mycobacterium tuberculosis* is a bacterium that infects 1/3 of the world today. While only 10% of infected individuals experience active tuberculosis disease, if left untreated infection results in death. The remainder of individuals harbor the bacteria in a clinically latent infection, and those individuals can experience reactivation of infection up to 10% per year. Our goal in a number of studies is to understand the role of the bacteria in initiating, sustaining and inhibiting the immune response during infection. Granulomas are a hallmark of tuberculosis infection arising within lungs of infected humans. So understanding first bacterial metabolic activity within granulomas, and second the role of bacterial inhibition of immune processes can help us better design therapies to control or clear infection. Understanding *M. tuberculosis* metabolism within granulomas could contribute to reducing the lengthy treatment required for tuberculosis and provide additional targets for new drugs. We present a multiscale *in silico* model of granuloma formation in tuberculosis. The model comprises host immunity, *M. tuberculosis* metabolism, *M. tuberculosis* growth adaptation to hypoxia, and nutrient diffusion. By mapping metabolite- and gene-scale perturbations to granuloma-scale outcomes and predicting mechanisms of sterilization, our method provides a powerful tool for hypothesis testing and guiding experimental searches for novel anti-tuberculosis interventions. Next, previous experimental studies suggest that *M. tuberculosis* inhibits a number of macrophage intracellular processes associated with antigen presentation. Specifically, we consider what purpose multiple mechanisms may serve, whether experimental protocols favor the detection of some mechanisms over others, and whether alternative mechanisms exist. In addition, based on a sensitivity analysis of the model, we identify other cellular processes that may be targeted by such pathogens to accomplish the same effect, representing potentially novel targets for therapies.

# Combined Metabolic Modeling and Population Modeling of Microbial Communities

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For environmental microbial communities, environment is destiny in the sense that, frequently, microbial community form and function are strongly linked to external chemical and physical conditions. Moreover, most environments outside of the lab are physically and chemically heterogeneous, further shaping and complicating the metabolisms of their resident microbial communities: spatial variation introduce physics such as diffusive and advective transport of nutrients and byproducts for example. Conversely, microbial metabolic activity can strongly effect the environment in which the community must function. Hence it is important to link metabolism at the cellular level to physics and chemistry at the community level.

In order to introduce metabolism to community-scale population dynamics, many modeling methods rely on large numbers of reaction kinetics parameters that are unmeasured and likely effectively unmeasurable (because they are themselves coupled to environmental conditions), also making detailed metabolic information mostly unusable. The bioengineering community has, in response to these difficulties, moved to kinetics-free formulations at the cellular level (e.g. flux balance analysis). These cellular level models should respond to system level environmental conditions. To combine and connect the two scales, we propose to replace classical kinetics functions (almost) entirely in community scale models and instead use cell-level metabolic models to predict metabolism and how it is influenced and influenced by the environment. The two scales are connected through exchange fluxes that are bounded by transport and thermodynamical constraints.

## Experimental and theoretical study of cancer plasticity: The effect of tumor microenvironment and long range interactions

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Cancer cells can undergo phenotypic cell state transitions in response to stochastically acquired genetic/epigenetic changes in genes or chemotherapy. Cell plasticity is also an important mechanism that allows cells to change their behaviour and role to effectively adapt to the microenvironment. Another explanation for cancer cell plasticity is known as the epithelial-to-mesenchymal transition (EMT). This talk will survey our recent experimental and mathematical approaches to study cell plasticity due to tumor microenvironment, in particular high interstitial fluid pressure (IFP). In addition, the collective behavior of dividing cancer cells which undergo chemotaxis will be presented. The results will be discussed in the context of the EMT.

## Numerical Optimization in Cancer Nanotherapy

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Computational cancer treatment models can enable the use of numerical optimization to quantify trade-offs and improve efficacy. They typically integrate multiple cellular and microenvironmental processes such as tumor growth, angiogenesis, and drug transport. In the optimization context, these computational models are used to evaluate the objective and constraint functions, whose gradients either are unavailable or require unreasonable effort to approximate with adequate precision due to various numerical issues. We therefore use the Mesh Adaptive Direct Search (MADS), a derivative-free optimization algorithm with rigorous convergence properties. We apply MADS to design drug-loaded nanoparticles targeting a 2D vascularized tumor model. We were able to generate nanoparticle sizes and ligand-receptor binding strengths that maximize nanoparticle accumulation as well as minimize tumor size. We further apply an advanced surrogate-assisted optimization strategy that speeds up the search process without compromising optimality. The presented framework of applying a rigorous optimization algorithm to a nanoparticle drug delivery model addresses major computational challenges and may facilitate decision-making in personalized cancer nanotherapy.

## Effect of synaptic cell-to-cell transmission on HIV recombination dynamics

Jesse Kreger (presenter)<sup>a</sup>, Natalia L. Komarova<sup>b</sup>, and Dominik Wodarz<sup>c</sup>

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In this talk, we investigate mathematical models regarding the evolutionary outcomes of human immunodeficiency virus (HIV), in humans. We analyze how the interplay between synaptic cell-to-cell transmission, free virus transmission, and the process of recombination affects the dynamics of an infection taking place. We first consider non-spatial models that take into account multiplicity of infection, co-infection, and competition between virus strains. We then introduce a novel agent-based model that takes into account the spatial nature of cell-to-cell transmission. We show that a combination of both free virus transmission and cell-to-cell transmission minimizes the time to a double hit mutant virus formation. We then analyze the growth and robustness of the double hit mutant virus population in the context of many different fitness landscapes and recombination rates.

## Determining harvest strategies of pheasants and biomass using an agent-based model

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Traditional row crop agriculture contributes to the degradation, fragmentation, and disappearance of wildlife habitat. There are conservation programs that encourage farmers to move some of their land out of row crop production and to instead grow perennial grasses, like switchgrass, on those lands to simulate natural habitat for wildlife. Additionally, management practices for perennial grasses can be less disruptive to reproductive processes of some wildlife, contributing to a better outcome for wildlife populations. Focusing on ring-necked pheasant populations in Iowa and the Conservation Reserve Program (CRP) plan meant to recover their population, we examine various spatial and temporal hunting and harvest strategies of pheasants and perennial grasses, respectively. We do this in order to determine an optimal harvesting strategy of both entities since pheasants are a popular game species that brings in lots of hunting tourism to Iowa and harvested CRP land can be sold as biomass feedstock. To this end, we build a spatially-explicit, agent-based model to simulate the dynamics associated with the pheasants, hunters, and tractors on a typical Iowa field region that includes land that has been enrolled in CRP. We examine and evaluate five different scenarios that vary spatial and temporal factors of both pheasant and biomass harvest in order to quantify the trade-offs between harvesting pheasants and biomass and determine spatial and temporal rules for harvesting. We also investigate the economic outcomes related to different harvesting strategies.

## Invasion reproductive numbers for discrete and periodic systems

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Just as the basic reproductive number (BRN)  $R_0$  measures a pathogen's ability to invade a completely susceptible population, the invasion reproductive number (IRN)  $\tilde{R}_0$  measures a pathogen's ability to invade a population where another infection is already resident. Recent work by the author and collaborators extends the definition of invasion reproductive numbers to periodic systems as well as discrete-time systems. In the former case, an application to Chagas disease shows that seasonality explains the observed co-persistence of two parasite strains in a single host population with cross-immunity, where an autonomous model predicts competitive exclusion. In the latter case, a simple two-pathogen model shows that the order of events affects the IRN but not the BRN, with the model exhibiting competitive exclusion under cross-immunity only for sufficiently small time steps.

## Predictive Mathematical Models of Hormone Treatment for Prostate Cancer

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Prostate cancer is commonly treated by a form of hormone therapy called androgen suppression. This form of treatment, while successful at reducing the cancer cell population, adversely affects quality of life and typically leads to a recurrence of the cancer in an androgen-independent form. Intermittent androgen suppression aims to alleviate some of these adverse affects by cycling the patient on and off treatment. Clinical studies have suggested that intermittent therapy is capable of maintaining androgen dependence over multiple treatment cycles while increasing quality of life during off-treatment periods. We present several mathematical models of prostate cancer growth to study the dynamics of androgen suppression therapy and the production of prostate-specific antigen (PSA), a clinical marker for prostate cancer. Biologically crude models were based on the assumption of an androgen independent (AI) cell population with constant net growth rate. These models gave poor accuracy when fitting clinical data during simulation. More refined models presented hypothesizes an AI population with increased sensitivity to low levels of androgen and these models generate high levels of accuracy in fitting clinical data. In general, we found that biologically more plausible models can forecast future PSA levels more accurately. These findings suggest that including more realistic mechanisms of resistance development may help predict the timing of androgen resistance.

## Are heart muscles affected by mitochondrial dynamics?

Adarsh Kumbhari<sup>a</sup> (presenter), Peter S. Kim<sup>a,\*</sup>, and Vijay Rajagopal<sup>b,\*</sup>

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Cardiomyocytes have evolved to have contained high mitochondrial density due to their unique energetic demands. These mitochondria form dynamic networks that are constantly undergoing fission and fusion events in response to a variety of stressors such as increased ATP demand or oxidative stress.

However, the precise bioenergetic roles that mitochondrial fission and fusion play are unknown. Previously, the Balaban group showed that mitochondria might split in an attempt to minimise the propagation of local dysfunction. Here, we use a validated hybrid agent-based-partial differential equation (PDE) model to quantify how different fission and fusion rates impact the distribution of ATP.

We find that mitochondria are robust to dramatically altered fusion and fusion rates in the short term, suggesting that there is more to the link between mitochondrial fission and fusion and ATP synthesis than what is in the literature. Moreover, mitochondrial dynamics are an increasingly popular target for the treatment of an ischaemia-reperfusion injury. A better understanding of the role of mitochondrial fission and fusion will be useful for such developments.

# Mathematical modeling about cancer combination therapy with immune checkpoint inhibitor

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\* Presenter

There has been much progress in recent years in developing checkpoint inhibitors, primarily PD-1 antibodies and PD-L1 antibodies. However, because of lack of tumor-infiltrating effector T cells, many patients in clinical trials do not respond to checkpoint inhibitor treatment. It was recently suggested that the combination of an immune checkpoint inhibitor and another anti-tumor drug, such as a cancer vaccine or BRAF inhibitor, may function synergistically to induce more effective antitumor immune responses. In this work, we considered the combination therapies of cancer with a checkpoint inhibitor and a cancer vaccine (or BRAF/MEK inhibitor) using mathematical models. Cancer vaccine activates dendritic cells so that they induce more T cells to infiltrate the tumor. BRAF kinase, is a key part of MAPK pathway of cancer cell proliferation. BRAF-targeted therapy induces significant responses in the majority of patients. We use mathematical models with systems of partial differential equations to explore the efficacy of the two drugs and compare the simulations with data from mouse experiments. The synergy map of combinations of an anti-PD-1 and a cancer vaccine shows that for optimal efficacy under MTD constraint, the level of dosage of anti-PD-1 should be related to the level of dosage of cancer vaccine as indicated by the optimal dose curve in the map. In contrast, the efficacy map of combination of an anti-PD-1 and a BRAF/MEK inhibitor shows that at large doses the drugs may become antagonistic: an increase in one of the drugs may actually result in an increase in the tumor volume.

## Monotonicity and Global Dynamics of a Nonlocal Two-species Phytoplankton Model

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We investigate a nonlocal reaction-diffusion-advection system modeling the population dynamics of two competing phytoplankton species in a eutrophic environment, where nutrients are in abundance and the species are limited by light only for their metabolism. We first demonstrate that the system does not preserve the competitive order in the pointwise sense. Then we introduce a special cone  $\mathcal{K}$  involving the cumulative distributions of the population densities, and a generalized notion of super- and subsolutions of the system in which the differential inequalities hold in the sense of the cone  $\mathcal{K}$ . A comparison principle is then established for such super- and subsolutions, which implies the monotonicity of the underlying semiflow with respect to the cone  $\mathcal{K}$ . As application, we study the global dynamics of the single species system and the competition system. The latter has implications for the evolution of movement for phytoplankton species.

# A multi-scale mathematical model of the innate immune response to respiratory fungal infections

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Invasive aspergillosis is among the most common fungal infections in immunocompromised hosts and carries a poor outcome. The spores of the causative organism, *Aspergillus fumigatus*, are ubiquitously distributed in the environment. Healthy hosts clear inhaled spores without developing disease, but individuals with impaired immunity are susceptible to a life-threatening respiratory infection that can then disseminate to other organs. The increasing use of immunosuppressive therapies in transplantation and cancer has dramatically increased suffering and death from this infection, and this trend is expected to continue. Current therapeutic approaches have been focused primarily on the pathogen, but a better understanding of host defenses in this infection may lead to the development of new treatments.

Iron is essential to all living organisms, and restricting iron availability is a critical mechanism of antimicrobial host defense against many microorganisms; conversely, successful pathogens have evolved potent mechanisms for scavenging iron from the host. These mechanisms have the potential to be harnessed therapeutically, for example with drugs that enhance the host's iron sequestration mechanisms. This talk presents a multi-scale mathematical model that can serve as a simulation tool of the role of iron in the innate immune response to invasive aspergillosis, and the exploration of host-centric therapeutic approaches.

## The local control theory of plant resource allocation

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A sophisticated model of plant growth needs to include components that determine the changing rates of photosynthate production and nitrogen uptake as the plant grows. These in turn depend on how resources are allocated to the different plant organs. Resource allocation is often assumed to be the result of a global (holistic) process geared toward optimizing growth; however, the physiological mechanisms are not known and there are theoretical difficulties in defining “optimal” growth. In this talk, we present an alternative theory of plant resource allocation based on local control; that is, we consider “roots” and “shoots” as though they were semi-independent organisms, each acting according to its own selfish interests. Surprisingly, the growth of such a model plant turns out to be optimal in an important sense, suggesting that global control of resource allocation in plants is unnecessary for models of plant growth and function.

# Identifying biological signals differentiating responders and non-responders in cancer immunotherapy

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The ability of biomarkers to predict which patient respond to immune checkpoint inhibitors has been inconsistent. For example, while PDL1 expression is positively correlated with a favorable outcome to treatment by anti-PDL1 in some solid tumors, it cannot clearly separate responders and non-responders in most situations. Here we use mechanistic modeling and machine learning to identify biological signals that could differentiate responders and non-responders to MPDL3280A (anti-PDL1) in non-small cell lung cancer (NSCLC).

We developed a mathematical model of cancer immunity in human, including interactions of immune cells, and modulation by the PD1, CTLA4 and TIGIT pathways. The model was calibrated using knockout and cell depletion mouse data, as well as human IHC and FACS data. We generated a population of >8000 virtual patients with high diversity in biology and patient phenotypes. The statistics of response was calibrated to match the response data of MPDL3280A in NSCLC from the BIRCH phase 2 trial. We then used Support Vector Machine analysis of the model parameters in the virtual population to identify differences in biology separating responders and non-responders.

Model predictions for the objective response rate as a function of PDL1 expression and of CD8+ T cell number match clinical data, providing confidence in the use of the model. Our analysis indicates that 7 biological processes related to NK cells, CTLs, tumor, Th1/IL2, PDL1 expression and drug PK can predict response with sufficient accuracy, when considered together. The predictive relationship is given by the machine learning model.

We generated a high diversity virtual population based on a mathematical model of cancer immunity. A machine learning analysis of the population led to a relationship predicting response to MPDL3280A in NSCLC. We now aim to translate this relationship into clinically measurable biomarkers.

# Application of impulsive differential equations to the case of yeast prion propagation, re-definition of the biological concept of propagon

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Yeast has emerged as a first choice model system for the study of amyloid-like propagation of prion proteins. One major reason is that, unlike their mammalian counterparts, yeast prions are not deleterious to the cells they reside in. Rather, prions in yeast are associated with harmless changes in phenotype. In recent decades the properties of these prions have been investigated in great detail. In yeast, the molecular mechanisms (replication and growth of aggregates) are coupled to cell population dynamics (cell budding) to sustain a stable concentration of aggregates at the colony level. In the early 2000's, yeast biologists introduced the concept of a "propagon" as the minimal prion structure or entity required for the faithful conversion of a full colony to the prion phenotype. The propagon definition was based on an experiment, curing of prion phenotypes under exposure to GdnHCl, that later became a staple for the study of prion propagation. However, defining the propagon as a particulate entity is limiting in terms of modeling, and it relies on the assumption that the aggregate dynamics are modeled by a system that is globally stable.

Our work aims to develop a quantitative basis for the definition of the propagon. We introduce a mathematical framework to study the evolution of continuous and deterministic concentrations under the effect of both molecular mechanisms and cell dynamics. Using impulsive differential equations, we are able to derive a simple model that exhibits the same qualitative behavior as observed in curing experiments. In order to obtain those characteristics, we need to relax some of the hypotheses on which the very concept of propagon relies on. In particular, the molecular mechanism must be represented by a multi-stable model. Our framework offers the potential to study any intracellular biochemical model and relate the results to experimentally measured quantities. The preliminary conclusions we draw have deep implications for the whole field of yeast prions, but also for amyloid-like processes in general.

## A West Nile Virus Model with Vertical Transmission and Periodic Time Delays

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Fuxiang Li is the presenter.

Seasonal change has played a critical role in the spatiotemporal dynamics of West Nile virus transmission. In this talk, we formulate and analyse a novel delay differential equation model, which incorporates seasonality, the vertical transmission of the virus, the temperature-dependent maturation delay, and the temperature-dependent extrinsic incubation period for mosquitoes. We first introduce the basic reproduction ratio  $R_0$  for this model, and then show that the disease is uniformly persistent if  $R_0 > 1$ . It is also shown that the disease-free periodic solution is attractive if  $R_0 < 1$ , provided that there is only a small invasion. In the case where all coefficients are constants and the disease-induced death rate of birds is zero, we establish a threshold result on the global stability in terms of  $R_0$ . Numerically, we study the West Nile virus transmission in Orange County, California, United States.

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## Title and abstract:

**Title:** Dynamical modeling of the transmission of African swine fever in a few earlier endemic sites in China

**Abstract:**

At present, African swine fever (ASF) is constantly bringing unprecedented difficulties and challenges to China's pig industry. There is urgent need to have an overall and deep perception on ASF for effective prevention and control in future.

In this talk, according to the local characteristics of ASF outbreak and epidemic in Xuanzhou District in Anhui province, China, we will present several dynamical models to study the mechanism of ASF outbreak in short-term transmission for a single closed farming unit (pigpen) or an area. With the data from the three selected typical epidemic sites (Guquan, Jinba, Liancheng) collected by Chinese Animal Health and Epidemiology Center, we will show the transmission power of the ASFV for each epidemic point by estimating some indicators, including incubation period (about 9-11 days), onset period (about 3 days), the basic reproduction number (about 7-14), the maximal number of pig infections per infected pigs per day (about 2-4). By studying endemic development in three sites, our findings suggest that ASF spreads rapidly and it is necessary to take culling measures timely for epidemic point. Considering some current measures (stopping movement, disinfecting, stopping swill and culling) implemented in China, our results also illustrate that, combined measures are more effective than any single measure and complete culling measure is considered to be the best efficacy and effectiveness to prevent the spread of ASF in the region under the existing conditions.

## Spatial Propagation of Nonlocal Dispersal Equations

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In this talk, I will report the spatial propagation for nonlocal dispersal equations. It consists of four parts. I first will present some relations between local (random) and nonlocal dispersal problems and then I will report our recent results on acceleration propagation for nonlocal dispersal systems. Part III is concerned with traveling waves and new types of entire solutions of nonlocal dispersal equations. In Part IV, I list some problems on nonlocal dispersal equations.

## Mathematical modeling in cancer immunotherapy

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\* Presenter

Cancer immunotherapy is intended to reactivate the body's own immune system to fight cancers. However, it is difficult to predict tumor responses, long term benefits, and remission via experiments or clinical trials, since it is such a new treatment. Thus, in this work, we combine mathematical modeling and biological experiments to help overcome these problems. In this talk, I will focus on two types of treatments: immune-checkpoint inhibitor and cytokine. For these treatments, we constructed PDE models to help clarify some controversial issue of CD200-CD200R complex treatment, and design treatment protocols to reduce side-effect and predict the long term benefits of the cytokine Interleukin-27 treatment.

# The Impact of Climate Warming and Spatial Heterogeneity on the Spreading of the West Nile Virus

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This talk deals with mathematical models describing the dynamic of West Nile virus in North America. For the spatially-independent WNv model, the usual basic reproduction number  $R_0$  is given and for the diffusive WNv model in a bounded domain, the basic reproduction numbers  $R_0^N, R_0^D$  are defined. To model and explore the expanding front of the infective region, a reaction-diffusion problem with free boundaries is proposed. The spatial-temporal risk index  $R_0^F(t)$ , which involves regional characteristic and time, is defined. Sufficient conditions for the virus to vanish or spread are given. Our results suggest that the spreading or vanishing of the virus depends on the initial number of infected individuals, the area of the infected region, the diffusion rate, and other factors. Moreover, we establish a new WNv model to describe the impact of climate warming and spatial heterogeneity.

## Statistical Methods for Reaction Network Inference

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Many interesting biological processes can be modeled as stochastic reaction networks. Prime examples of their applications are in modeling epidemic spread and biochemical reactions. Fitting these models to experimental data, sometimes called model calibration, is a challenging problem. I will discuss methods we have developed to tackle some of these challenges. The methods presented include an algebraic one, those based on regularization, and more recently approximate Bayesian methods based on notion of synthetic likelihood. I will present some results on real data sets, one from a regeneration experiment in the zebrafish, and another from the plague outbreak at Eyam, Derbyshire England from 1665-1666.

## Boundary Homogenization of Patchy Membranes and the Roles of Clustering in Chemoreception

Alan Lindsay<sup>a</sup>(presenter) and Andrew J. Bernoff<sup>b</sup>

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Cells interact with their environment and communicate with other agents through contact with diffusing signaling molecules at receptor sites distributed on the cellular surface. For this process of chemoreception to be effective in such a noisy environment, surface receptors must be numerous and widely distributed. The spatial organization or 'clustering' of these receptors has long been known to play a key biophysical role, however, mathematical analysis of this role is a challenging problem that, despite much attention, is not yet resolved.

In this talk I will describe new theoretical results, which give precise information of the role of clustering in scenarios where receptors occupy spherical surfaces or are periodically arranged on infinite planes. With these new results, optimizing configurations of receptors can be identified. In the case of a plane with a periodic arrangement of receptors, we find that a hexagonal configuration maximizes the sensing rate of the receptors.

In addition, we will discuss a new suite of Kinetic Monte Carlo methods for diffusive signaling problems. These methods are able to verify theoretical results and in addition allow for efficient exploration of the space of receptor clustering configurations.

# Intra-specific Competition and Insect Larval Development: a Model with Time-dependent Delay

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We derive a stage-structured model for an insect population in which a larva matures on reaching a certain size, and in which there is intra-specific competition among larvae that hinders their development, thereby prolonging the larval phase. The model, a system of delay differential equations for the total numbers of adults and larvae, assumes two forms. One of these is a system with a variable state-dependent time delay determined by a threshold condition, the other has constant and distributed delays, a size-like independent variable replacing time  $t$ , and no threshold condition. We prove theorems on boundedness and on the linear stability of equilibria.

## Modeling immune system in application to studying IBD and TB infection

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\* Presenter

T cell-mediated immune system has to maintain both a state of tolerance toward commensal bacteria and to protect the host from pathogens. The interaction of macrophages and T cells plays an important role in the immune response in different types of diseases. In this talk, I will discuss how to model the dynamics and the intersection of macrophages, T cells, and their cytokines, in application to studying two types of diseases, inflammatory bowel disease (IBD) and TB infection. The models provide a conceptual framework as a basis for future investigations, in order to develop an *in-silico* tool for disease prognosis and treatment decisions, such as for CAR-T cell therapy which is an immunotherapy that strengthens the power of a patient's own immune system to attack tumors.

## Modeling the immunological consequences of radiation therapy

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Fractionated radiotherapy regimes routinely used in clinical practice attempt to completely eradicate tumors by the direct lethal effect of radiation on cancer cells. Although this form of prescribing radiotherapy has been demonstrated to be effective in many patients, locoregional recurrence still remains a major cause of mortality. There is now considerable evidence supporting the ability of radiotherapy to induce not only local but also systemic antitumor immune responses as a result of immunogenic cell death. Although the possibility of intentionally induce efficient antitumor immune responses with radiotherapy is of high clinical interest, there are still many unanswered questions regarding the underlying immuno-oncological processes and dynamics for such strategy to be feasible. For instance, more comprehensive knowledge about the radiation-immune system synergy and the dependence of radiation-induced antitumor immunity on pre-treatment tumor features and microenvironmental factors is still needed. Mathematical modeling is a promising avenue for addressing the aforementioned challenges as I will show in this talk. Here I will describe a variety of mathematical models that we develop to study the immunological consequences of radiotherapy and discuss their main results as well as potential clinical implications.

## A stochastic multi-scale model of *Francisella tularensis* infection

Carruthers J<sup>a</sup>, López-García M<sup>\*,a</sup>, Gillard JJ<sup>b</sup>, Laws TR<sup>b</sup>, Lythe G<sup>a</sup> and Molina-París C<sup>a</sup>

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We present a multi-scale model of the within-phagocyte, within-host and population-level infection dynamics of *Francisella tularensis*, which extends the mechanistic one proposed by Wood et al. (2014). Our multi-scale model incorporates key aspects of the interaction between host phagocytes and extracellular bacteria, accounts for inter-phagocyte variability in the number of bacteria released upon phagocyte rupture, and allows one to compute the probability of response, and mean time until response, of an infected individual as a function of the initial infection dose. A Bayesian approach is applied to parameterize both the within-phagocyte and within-host models using infection data. Finally, we show how dose response probabilities at the individual level can be used to estimate the airborne propagation of *Francisella tularensis* in indoor settings (such as a microbiology laboratory) at the population level, by means of a deterministic zonal ventilation model.

This talk is based on the paper

Carruthers J, López-García M, Gillard JJ, Laws TR, Lythe G, Molina-París C (2018) *A novel stochastic multi-scale model of Francisella tularensis infection to predict risk of infection in a laboratory*. Frontiers in Microbiology, 9: 1165.

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## Temperature-dependent mosquito mortality and effects on Chikungunya virus transmission

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### **Presenter: Cynthia C. Lord**

Chikungunya virus (CHIKV) is primarily transmitted by 2 mosquito species, *Aedes aegypti* and *Aedes albopictus*. This virus can cause serious and debilitating disease and there is no vaccine. Transmission and outbreaks have occurred in many countries, and introductions into Florida and the US can occur during outbreaks elsewhere. Local transmission occurred in Florida, raising questions about the factors influencing successful introductions. These mosquitoes have similar habitats, but differ in their response to environmental factors and in their human-biting behavior. Multiple strains of the virus occur, with differential infectivity for the 2 mosquito species. Both mosquito species are present in Florida, but relative population sizes vary. Using a deterministic 2-vector model of the transmission dynamics, we investigated what factors most influence the likelihood of epidemics following introduction. Changing the relationship between mosquito mortality and temperature altered the relative importance of other factors, including the importance of *Ae. albopictus*. As was expected, overall model results supported *Ae. aegypti* as the dominant vector. However, *Aedes albopictus* could support outbreaks, particularly of the viral strain adapted to this species.

## Population growth with continuous and non-continuous development durations

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When describing the vector-borne disease transmission, sometimes, the stage-structure of the vector population growth should be incorporated. This talk will present two models derived for describing population growth with differentiable development duration and non-continuous maturation delay. The model analysis involves theories of infinite dynamical systems. Numerical simulations will further be presented.

## Ideal free distribution in Two patches

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We will discuss some recent progress on the ideal free distribution (IFD) in patch models, with the emphasis on two patches. Dispersal strategies leading to the IFD of organisms are generally evolutionarily stable. Applications to river models will be given. We will also discuss the existence of evolutionarily stable dispersal strategies when dispersal strategies do not lead to the IFD.

# Modeling the heterogeneity of EMT network dynamics with single cell RNA-seq data

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Epithelial-mesenchymal transition (EMT) plays a crucial role in embryonic development and tumorigenesis. Although EMT has been extensively studied with both computational and experimental methods, the gene regulatory mechanisms governing the transition are not yet well understood. Recent investigations, however, have begun to better characterize the complex phenotypic plasticity underlying EMT using a computational systems biology approach. Here, we analyzed recently published single-cell RNA sequencing (scRNA-seq) data from eight organs and tissues of E9.5 to E11.5 mouse embryos and identified the gene expression patterns of both epithelial and mesenchymal phenotypes, as well as a hybrid state. By integrating the scRNA-seq data and gene regulatory interactions from the literature, we constructed a gene regulatory network model governing the decision-making of EMT in the context of the developing mouse embryos. We simulated the network using our recently developed mathematical modeling algorithm, named RACIPE, and observed three distinct phenotypic states whose gene expression patterns can be associated with the epithelial, hybrid, and mesenchymal states in the scRNA-seq data. The role of the Wnt signaling pathway in inducing EMT was revealed by the behavior of the simulated network and gene ontology analysis of the gene expression data. A more comprehensive understanding of the mechanisms of EMT at the cellular level will illuminate the processes of tumorigenesis and metastasis, facilitating the development of targeted diagnostic assessments and treatments.

## Near-criticality in mathematical models of epidemics

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In an epidemic model, the basic reproduction number  $R_0$  is a function of the parameters (such as infection rate) measuring disease infectivity. In a large population, if  $R_0 > 1$ , then the disease can spread and infect much of the population (supercritical epidemic); if  $R_0 < 1$ , then the disease will die out quickly (subcritical epidemic), with only few individuals infected.

For many epidemics, the dynamics are such that  $R_0$  can cross the threshold from supercritical to subcritical (for instance, due to control measures such as vaccination) or from subcritical to supercritical (for instance, due to a virus mutation making it easier for it to infect hosts). Therefore, near-criticality can be thought of as a paradigm for disease emergence and eradication, and understanding near-critical phenomena is a key epidemiological challenge.

In this talk, we explore near-criticality in the context of some simple models of SIS (susceptible-infective-susceptible) epidemics in large homogeneous populations.

# Movement behaviour of fish, harvesting-induced habitat degradation and the optimal size of marine reserves

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Marine reserves have been proposed and implemented to simultaneously protect fish stocks and increase fisheries' yield. How well reserves perform these two roles depends also on how fish move into and out of them. The harvesting process itself often decreases habitat quality outside marine reserves and thereby influences the movement behaviour of fish. Our work explores the effects of this feedback on the function and optimal size of marine reserves. Our model is based on reaction-diffusion equations and recent advances in their application to strongly heterogeneous environments with sharp transitions in environmental conditions. We model movement behaviour in response to harvesting and habitat destruction via increased diffusion rates and increased preference for protected areas, and implement reduced reproduction as an effect of habitat degradation. We find that movement-behavioural responses of fish to harvesting can decrease the economic value of protected areas and increase their conservation value. For the maximum sustainable yield outside a reserve, we find that a low harvesting rate and small protected area are optimal when fish show a strong preference for protected areas as a response to fishing efforts. On the other hand, a high harvesting rate and a large protected area are optimal if fish respond to harvesting by a strong increase in movement rates in fishing areas.

## Mathematically Describing how Firing Rate Heterogeneity Modulates in Cortical Networks

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The level of firing rate heterogeneity in a population of cortical neurons has consequences for how stimuli are processed. Studies have shown that the right amount of firing rate heterogeneity (not too much or too little) is a signature of efficient coding, thus quantifying the relative amount of firing rate heterogeneity is important. Too often the level of firing rate heterogeneity is imposed rather than derived from the nonlinear interactions of neural attributes. We have shown how the relationship between intrinsic and network attributes leads to different levels of heterogeneity depending on regime by employing dimension reduction methods to derive formulas for these dynamics. We further show theoretically how accounting for realistic intrinsic dynamics in neural oscillators can modulate firing rate heterogeneity in non-intuitive ways. Finally we apply our theory to the feedforward electrosensory system of weakly electric fish, where we demonstrate how connectivity rules can lead to qualitatively similar statistics as the experimental data. We predict that stimulus tuning is related to the effective network architecture or connectivity. Thus, neural attributes do not act in a linear manner but rather in a complex stimulus-dependent fashion to modulate heterogeneity and thus shape population codes.

## The impact of edge behaviour on population persistence in a moving habitat model

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The earth's climate is warming, and as a result, many species habitat ranges are shifting. The shift in habitat ranges threatens the local persistence of these species. Mathematical models that capture this phenomenon of range shift do so by considering a favourable bounded domain that has a time dependent location on the real line (moving-habitat models). In most of these models, density is considered to be continuous across the boundaries. However, it has been shown that many species exhibit particular behaviour at habitat edges, such as biased movement towards the more suitable habitat. We introduce an extension of previous models by generalizing the boundary conditions to capture such individual behaviour. Under these generalized conditions, the density may not be continuous across a boundary. We obtain persistence conditions that show that the behaviour at the trailing edge plays a crucial role in the species' ability to persist. A species that can sense the trailing edge, and respond to it, may be able to persist for arbitrarily fast moving habitats. We illustrate our theoretical results with numerical solutions of the system.

# Modeling the mechanosensitivity of nascent adhesion formation

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Cellular migration is a tightly regulated process that involves the actin cytoskeleton, adaptor proteins, integrin receptors, and extracellular ligands. Forces are transmitted extracellularly through complexes of these molecules called adhesions. To understand the dynamics and mechanosensitive properties of nascent adhesions (NA), we developed a biophysical model of NA's as co-localized clusters of integrins and adaptor proteins. The model is then analyzed to characterize the dependence of NA area on biophysical parameters that regulate the number of integrins and adaptor proteins within NA through a mechanosensitive co-aggregation mechanism. Our results reveal that (i) NA formation is triggered beyond a threshold of integrin, ligand, or adaptor protein densities, (ii) that an increase in co-aggregation potentiates NA formation, and (iii) that mechanical stress plays a key role in regulating assembly/disassembly during the NA life-cycle through a bistable-switch possessing a hysteresis. Stochastic simulations of the model confirm these results computationally. This study extends the results of previous models of adhesions as a collection of integrin-ligand bonds under force, providing insight into the joint chemical and mechanical conditions that produce NA assembly and disassembly.

# Single-cell approaches to unravel the developmental trajectories of cells

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Single-cell RNA sequencing technologies present great potential to gain insight into developmental processes, given appropriate models and analysis tools. Significant challenges present themselves in the analysis and interpretation of these data, given the dimensionality and prevalent heterogeneity. While progress on tasks such as cell clustering and trajectory inference has been made, a major remaining gap is the integration of dynamical models with the analysis of data-derived cell states. A necessary prerequisite to such integration is sufficient description of the cell states and their interactions: we introduce methods to accomplish this via optimization. We then describe how models of molecular or cellular networks can be derived from data, analyzed via stability theory, and fit to data via Bayesian parameter inference. These provide insight the dynamics and regulatory mechanisms that control embryonic development and stem cell differentiation.

## A personal view of modeling hematopoietic regulation

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This talk will be a highly personal and idiosyncratic accounting of my view of the modeling of hematopoietic regulation starting in the early 1970's and extending to today.

I intend to highlight the perils and pitfalls of this type of endeavour with examples from my own follies as well as to showcase the successes that have been had through the years. Though the examples are drawn from one specific field of biomathematics, the lessons and cautionary tales are more or less universal, illustrating the maxim of the sensible (realistic) theoretician that "All models are wrong".

Finally I wish to pay homage to the many talented collaborators who have traveled with me on this journey spanning almost 50 years and brought joy to my scientific life.

## Cloud-hosted mathematical models: links between education, research, and outreach

Randy Heiland<sup>a</sup>, Daniel Mishler<sup>a,†</sup>, Tyler Zhang<sup>a,†</sup>, Eric Bower<sup>a,†</sup>, and Paul Macklin<sup>a,\*</sup>

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To address the challenges facing undergraduate research, we tested lab structure that can scalably involve undergraduates in cutting-edge mathematical biology research. Teams of two-to-four undergraduates are jointly mentored by a graduate student (or senior personnel) and the lab’s principal investigator. Graduate students gain extra help and team management experience, while undergraduates gain modeling experience and co-author scientific papers. Each team is responsible for a new methodology or a new mathematical model of a specific biological problem. All teams “cross-pollinate” at weekly lab meetings that combine short progress reports, discussion, and unstructured mentoring time.

We present a case study: a team developed `xml2jupyter` [1] to automatically convert command-line agent-based models (written in `PhysiCell` [2]) to cloud-hosted, interactive models on `nanoHUB` [3]. This tool reduced the time to create and deploy a graphical user interface from months to hours, allowing us to expand the scope and productivity of grant-funded projects. Rapidly-developed, cloud-hosted mathematical models have enabled new approaches to education (adaptive lesson plans; student portfolio pieces), research (research papers with online model demos), and outreach (sharing interactive models on social media). With further refinement, we expect that heavy undergraduate research participation will continue to drive unexpected results that benefit education and research. For an example of a cloud-hosted mathematical model [4], see <http://nanohub.org/tools/pc4cancerimmune>.

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## Oscillations in Gene Regulatory Networks: The Importance of Spatial Aspects

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Transcription factors typically exert control over molecular levels through feedback mechanisms - proteins bind to promoters in the nucleus and either up-regulate or down-regulate production of mRNA. Many gene regulatory networks (GRNs) contain negative feedback loops whereby promoter binding by proteins reduces the transcription rate of a gene. This can be either direct and self-repressing if the promoter binding affects the protein's own gene, or indirect if the effect is on a subsequent gene in a given network. Typically, negative feedback leads to mRNA and protein levels oscillating over time but also spatially since the molecules must move between the nucleus and cytoplasm. In the models presented in this talk I shall focus on capturing this oscillatory spatio-temporal behaviour. Firstly, I consider a PDE model of the Hes1 system in order to investigate the importance of spatial aspects, specifically diffusion and the location of gene and protein production sites. I will then show how the model may be easily extended to examine spatio-temporal models of synthetic GRNs e.g. n-gene repressilators and activator-repressor systems. Finally, I will formulate and analyse stochastic spatio-temporal models of such synthetic GRNs which connect more accurately with both the underlying biology (by incorporating promoter binding) and experimental data (such systems are observed to be noisy and in many cases the actual numbers of molecules involved are quite low).

## Vaccine impact in homogeneous and age-structured models

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The dynamics of vaccine-preventable diseases depend on both the underlying disease process and the nature of the vaccine. Here we present the impact of different types of imperfect vaccines on structured populations. Four vaccine parameters are considered: three affect the susceptibility of vaccinated individuals to infection (“leakiness”, primary vaccine failure and waning of vaccine-derived immunity), and one reflects the relative reduction in infectiousness of vaccinated individuals who get infected. We derive analytic bounds to the overall reduction in transmission due to vaccination based on these parameters. We also show that this reduction is larger in models with age-structured contacts in which children are assumed to have more contacts than adults.

## Parameter Sensitivity in Models for Erythropoiesis and Thrombopoiesis

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Age-structured models for erythropoiesis and thrombopoiesis have been developed. The models provide detailed information about critical biochemical and developmental processes in the maturation of these hematopoietic cell lines. These models have a large number of parameters associated with key elements in these physiological processes. These parameters govern the dynamics of the models and can indicate the state of health or disease from the model behavior. Some parameters are readily measured from existing experimental studies, but many of these parameters are difficult to measure through direct studies, so are computed numerically.

We have performed extensive sensitivity analysis of the parameters in the models. Some parameters are very robust over a range of values, indicating evolutionary stability in the processes they represent. However, other parameters are more sensitive and suggest mechanisms for potential disease. We explore different parameter regimes and compare to actual patient data. Our bifurcation studies of the models suggest potential problems in these hematopoietic processes that support certain theories for existing diseases. The parameters that lead to oscillatory behavior provide a greater insight into key mechanisms in these processes and are potential targets for future therapies.

## Cell migration in immunity

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Immune cells are the only cells capable of migrating around the body in a healthy adult, trafficking from blood into any infected tissue by utilizing an amoeboid form of cell movement to navigate 3D microenvironments. This dynamic spatial and temporal behaviour is critical to immune function - heritable defects in cell migration cause severe immunodeficiencies, impacting both immune cell homeostasis and immune surveillance. We use microscopy approaches to track immune cells in space and time, observing them in their natural environments and in settings where we can precisely control the physical constraints they encounter, in order to shed light on the complex choreography of immune cells that is critical to raising effective immune responses and maintain constant immune population sizes over time.

## Population-level consequences of symbiosis in a stage-structured energy budget model

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Physiologically structured population models (PSPMs) provide a link between individual-level processes and population dynamics. PSPMs are formulated using functions that represent the life history of the individuals as demographic rates relative to their environment. The demographic rates in PSPMs usually offer a mechanistic representation based on age, size, or sex. However, these rates have a limited ability to describe metabolic aspects of the organisms. Here, we use dynamic energy budget (DEB) theory to build a PSPM that explicitly includes energy acquisition and allocation at different stages of an organisms' life cycle. We formulate the PSPM model deriving the demographic rates from a DEB model, including individual energy storage, structural biomass, and maturity.

We use our DEB-PSPM model to elucidate the population-level consequences of trophic symbiosis in thyasirid bivalves. Thyasirid bivalves are particulate feeders, obtaining nutrients from free-living chemosynthetic bacteria. However, some species are symbiotic and harbour bacteria in enlarged gills. Symbiotic thyasirids are mixotrophs, digesting symbiotic bacteria as an additional resource. We compare two closely related and sympatric species: *Thyasira* cf. *gouldi*, which is symbiotic, and *Parathyasira* sp., which is asymbiotic. We highlight how the symbiotic association is likely to change the energy budget of a mixotrophic bivalve and thereby determine the population dynamics, which is of interest in a wide range of trophic symbioses.

# METHODS FOR DERIVING NECESSARY AND SUFFICIENT CONDITIONS FOR BACKWARD BIFURCATION

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Backward bifurcation has significant implications for disease control. Deriving necessary and sufficient conditions for backward bifurcation is of paramount importance to understand the reasons for its occurrence and devise effective control strategies. We review the methods that lead to necessary and sufficient conditions for backward bifurcation in infectious disease models, particularly ones that apply to age-since-infection structured PDEs. We further propose a new method, applicable to both ODEs and PDEs. We illustrate the methods on a novel ODE model of cholera with vaccination and its age-since-infection structured version.

## Remote Sensing, Weather, and Demographic Data for Mosquito-Borne Disease Risk

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Mosquito-borne diseases such as Zika, dengue, and chikungunya viruses have dynamics coupled to weather, ecology, human infrastructure, socio-economic demographics, and behavior. We use time-varying remote sensing and weather data, to predict risk through time for dengue outbreaks in Brazil using statistical methods. Our statistical model indicates that the relationships between the variables are complex, but that quantifying risk is possible with the right data at appropriate spatio-temporal scales. We show that important ecological variables and disease risk vary with geography across the country. Ecological drivers exhibit low and high frequency behavior that change risk locally with lags in time.

## Quantifying drug distribution and response dynamics in experimental glioblastoma

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Glioblastoma (GBM) diagnosis carries a dismal prognosis, and despite hundreds of clinical trials, the standard of care has remained largely unchanged for over a decade. Poor clinical trial outcomes for GBM may be attributed to multiple causes, including therapeutic resistance of tumor cells and inadequate distribution of drug due to restrictions imposed by the blood brain barrier (BBB). Using bioluminescence imaging (BLI) data from preclinical studies with patient-derived xenografts (PDXs) treated with the investigational drug, depatuxizumab mafodotin (also known as ABT-414), we sought to determine whether we might be able to tease apart the contributions of these factors to observed differences in therapeutic response. To do this, we first developed a minimal mathematical model of GBM growth and therapeutic response, consisting of a system of three ordinary differential equations. These equations represent sensitive and resistant cell populations and the level of drug, with terms accounting for the degree of drug exposure and sensitivity among the cell populations. Next, we investigated the sensitivity of our model to parameters, using Latin hypercube sampling and partial rank correlation coefficients. Finally, using the BLI data from treated and untreated PDXs grown in either the flank or intracranial setting, we estimated parameter values for each subject using a least squares regression to fit the model to the data. These parameter estimates indicate heterogeneity in both the degree of BBB breakdown as well as in the prevalence of resistant cells across PDX cell lines. Further, our model results suggest that better outcomes in response to drug were more highly associated with improved drug distribution than a lower preponderance of resistant cells. While further experiments are needed to confirm this, our results suggest that accounting for drug distribution could vastly improve analyses of clinical trial results and that enhancing drug delivery could make great strides in improving patient outcomes.

## Modeling the role of motile cells in biofilm ecology

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The establishment of mixed species biofilms results from the interplay of different factors, such as mass transfer, detachment forces, communication (typically via quorum sensing), and metabolic cooperation or competition. Recent advances in microbial ecology have identified motility as one of the main mediators of the development and shape of multispecies communities. Indeed, motile cells with high kinetic energy and acting as invaders can lead to the dissolution of heterologous biofilms and re-population of the matrix, or can result in the development of several beneficial phenotypes. To fill in the gap in modeling the establishment of such mixed species communities mediated by the invasion process, a one-dimensional continuous model is developed by considering two state variables representing the planktonic and sessile phenotypes and reproducing the transition from one state to the other. Different planktonic cell motion behaviors can be described, as well as by including regulatory regimes triggered by the external chemical dynamics. The proposed model is solved numerically to simulate biofilm evolution during biologically relevant conditions and provides interesting insights towards the qualitative and quantitative understanding of biofilm dynamics and ecology.

## Teaching reflections after one year on the tenure-track

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Teaching full-time at a private liberal arts college after sparsely teaching at large public land-grant universities has required learning, relearning, and unlearning of many pedagogical practices. This talk will take you swiftly through a whirlwind first year and cover lessons learned from hiccups with active classroom assignments; share some favorite tips and tricks gained from MAA Project NExT and reading “The Black Academic’s Guide to Winning Tenure Without Losing Your Soul”; and also describe how an interest in Ignatian Pedagogy unexpectedly began. Finally, we will discuss plans for refining post-exam reflection writing assignments, establishing a departmental Matlab code repository, and building a research army of undergraduate math biologists during years 2 and beyond.

# Computational analysis of mechanism of action of bispecific antibodies for cancer treatment

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Bispecific antibodies are versatile therapeutic platform, especially for cancer immunotherapy as they could be adapted to target various cell types of interest across different malignancies. The development of these bispecifics can greatly benefit from having an quantitative framework to elucidate the role of their molecular properties in determining their clinical performance. Here, we describe a theoretical analysis of the key mechanisms governing their efficacy using a computational modeling approach.

Our model is a mathematical abstraction of the complex network of interactions between the bispecifics and the cells that they interact with, along with the key components of the cellular feedback machinery. We start with first step of receptor binding with the dual targets, and probe the system using model simulations in the context of cancer treatment bispecifics. In particular we focus on formation of the immune-synapse whereby the cancer and the immune cells are brought together due to binding with the bispecific antibody. We explore the role of the binding kinetics, and the target expression and the heterogeneity therein with an aim to get a theoretical understanding of the kinetics of the immune-synapse formation. Next we include the mathematical equations describing the downstream events of immune cell activation, proliferation and the cancer cell lysis to link the properties of the bispecific to the eventual efficacy. We also explore the role of the typical positive and negative feedback loops associated with their action, and how it influences the dynamical behavior of the system.

Our analysis sheds light into the dynamical behavior of the bispecific action and attempts to elucidate the interplay of various system parameters associated with strength of immune system, disease burden and progression and bispecific drug properties and can pave the way to improvements in the drug design and treatment strategies.

## Optimal Control of Mixed Treatments for Retinitis Pigmentosa

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Retinitis Pigmentosa (RP) is a degenerative eye disease affecting millions of people worldwide. This presentation will begin with a brief background on RP and previous work done on the mathematical modeling of two treatments for RP: Rod-derived Cone Viability Factor (RdCVF) and Mesencephalic-Astrocyte-derived-Neurotrophic Factor (MANF). We will then introduce an optimal control model mixing both RdCVF and MANF treatments. Numerical results are presented and discussed.

## Absolute Concentration Robustness: Algebra and Geometry

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How do cells maintain homeostasis in fluctuating environments? Investigations into this question led Shinar and Feinberg to introduce in 2010 the concept of absolute concentration robustness (ACR). A biochemical system exhibits ACR in some species if the steady-state value of that species does not depend on initial conditions. Thus, a system with ACR can maintain a constant level of one species even as the environment changes. Despite a great deal of interest in ACR in recent years, the following basic question remains open: How can we determine quickly whether a given biochemical system has ACR? Although various approaches to this problem have been proposed, we show in this talk that they are incomplete. Accordingly, we present a new method for deciding ACR, which uses computational algebra. We illustrate our results on several biochemical signaling networks.

## Towards a Multiscale Model of the Bone Microenvironment in Multiple Myeloma

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Multiple myeloma is a plasma cell malignancy that is treatable but largely incurable, and often causes bone pain due to extensive bone destruction. The main obstacle to effective treatment is the failure to completely eradicate the disease, which is due to many cell intrinsic and extrinsic mechanisms including intra-tumor heterogeneity, the protective effect of the stroma, and cancer cell dormancy. Of those, myeloma cell dormancy is the least understood. During dormancy, external signals in the bone niche suppress the active proliferation of the tumor cells, causing resistance to cytotoxic therapies that target dividing cells. On the other hand, mechanisms driving bone remodeling cause dormant myeloma cells to reawaken, leading to tumor relapse. Because myeloma cell dormancy is reversible, manipulation of the mechanisms that control dormancy has the potential to impact the progression of disease.

We develop a hybrid agent-based model that incorporates key cell types that drive normal bone remodeling, including osteoclasts, which break down bone, and osteoblasts, which form new bone. These cells are modeled as agents on a grid that move and respond to molecules that diffuse in the microenvironment, including RANKL and TGF-beta. We focus on these mechanisms due to their role in normal bone remodeling as well as the “vicious cycle” that results in excessive bone resorption and enhanced survival of myeloma cells.

Working closely with biologists, we carefully parameterize the agent-based model to reproduce normal bone remodeling dynamics. We then explore the impact of dormant cell reawakening on cancer growth rates at different stages of osteolytic bone disease. This model provides a foundation for predicting the impact of dormant myeloma cells in disease progression in order to understand how to improve treatment outcomes.

## Can random fluctuations reconcile competitive exclusion with biodiversity?

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Analysis of classic models of competition between two species support the principle of competitive exclusion and suggest that coexistence, and therefore biodiversity, is either unlikely or impossible. However, biodiversity is commonly observed in nature. In this talk, we develop and analyze continuous time Markov chain (CTMC) counterpart models related to the classical Lotka-Volterra model of competition and exploitative competition for a single non-reproducing essential resource in a chemostat, respectively. In order for an invader to be able to invade a resident species at the single species equilibrium in deterministic models, the equilibrium must be unstable toward the interior of the phase space with respect to the linearized system. That is, the eigenvalue of the associated eigenvector changes sign from negative to positive. Using this fact, an invasion number  $\mathcal{I}_0$  is determined for each model such that  $\mathcal{I}_0 < 1$  implies the resident species cannot be invaded and  $\mathcal{I}_0 > 1$  guarantees the resident will be invaded. Inspired by recent results in epidemiological models, it is shown that the duration of a doomed invasion (an invasion which fails before reaching a significant population size) increases as  $\mathcal{I}_0$  approaches 1. Implications for reconciling competitive exclusion and biodiversity are discussed.

## Transcription regulation as a cellular decision making process: the NF- $\kappa$ B case study

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Transcription regulation plays a major role in the process by which single cells dynamically assess the internal and external conditions to appropriately adjust their function. For example, the NF- $\kappa$ B protein complex can sense a variety of different signals related to inflammation, stress, temperature, and radiation, in order to appropriately adjust the transcription regulation of a large number ( $> 500$ ) of different genes. This highly stochastic process that involves a large number of non-linear, stochastic interactions can be thought as a decision making process for the cell. Here, the cell uses the dynamics of the transcription factor and its functional relation to effector genes to decide whether to activate pathways that ultimately lead to outcomes such as cell death, healing, or growth. This talk will present a stochastic model for describing the dynamics of oscillatory transcription regulation. We will discuss a theoretical framework that uses this stochastic model to study the ability of any regulatory network, and in particular NF- $\kappa$ B, to simultaneously sense multiple signals and take multifaceted decisions.

## Recent applications of Modeling and Simulation in Drug Development: From Data to Decision

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Mechanistic modeling and simulation (M&S) has been a core component of model-informed drug discovery and development, accelerating and improving decision making in the development and utilization of safe and effective new medicines for patients in need. This talk will give two recent cases of modeling and simulation from GSK, one of leading Pharmaceutical companies in embedding M&S in drug development.

Decoys and dilution: the impact of incompetent hosts  
on prevalence of Chagas disease

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Biodiversity is commonly believed to reduce risk of vector-borne zoonoses. This study focuses on the effect of biodiversity, specifically on the effect of the decoy process (additional hosts distracting vectors from their focal host), on reducing infections of vector-borne diseases in humans. Here, we consider the specific case of Chagas disease and use mathematical population models to observe the impact on human infection of the proximity of chickens, which are incompetent hosts for the parasite but serve as a preferred food source for vectors. We consider three cases as the distance between the two host populations varies: short (when farmers bring chickens inside the home to protect them from predators), intermediate (close enough for vectors with one host to detect the presence of the other host type), and far (separate enclosed buildings such as a home and hen-house). Our analysis shows that the presence of chickens reduces parasite prevalence in humans only at an intermediate distance and under the condition that the vector birth rate associated with chickens falls below a threshold value, which is relative to the vector birth rate associated with humans and inversely proportional to the infection rate among humans.

# Applying the chemical-reaction definition of mass action to infectious disease modelling

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The law of mass action governs interactions between susceptible and infected individuals in a variety of infectious disease models. However, the commonly used version is a simplification of the law of mass action originally used to describe chemical reactions. Here, we generalize a disease model using the chemical-reaction definition of mass action in both an altered transmission term and an altered recovery term in the form of positive exponents. For this generalized model, we examine the long-term outcome as these exponents vary. We found conditions for the existence and uniqueness of the endemic equilibria under a variety of possible exponents. We also determined conditions under which backward bifurcations are possible. The implications of these findings imply that the simplified form of mass action may be masking complex behaviour that would be captured by generalized mass action. This may lead to a loss of predictability in some models.

## Modelling the evolution of viral oncogenesis

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One in 10 cancers is believed to be caused by an oncovirus. Yet the vast majority of infections by these viruses do not progress to cancer and mortality. Given their potent oncogenes, it is unclear why these viruses are not more virulent. We investigate oncovirus oncogenicity from a virulence evolution perspective. Anchoring on a generic cell life cycle model, we model idealised life cycles of human oncoviruses and study the selective pressures for and against oncogenesis. Embedding this within-host model in a between-host model allows us to investigate trade-offs that couple these two levels. Surprisingly, we find that while viruses that cause more cancer produce more virions during an infection, they in fact have a lower overall fitness. In addition to general findings like this one that apply across (large DNA, small DNA and retro-like) virus groups, we also find that certain specifics can matter. For instance, we show that the life cycle of small DNA viruses allow for the evolution of strategies with higher cancer risk; consistent with the prominent example of human papillomaviruses.

# Biophysically-based circuit modeling of large-scale brain dynamics: applications for computational psychiatry

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Noninvasive neuroimaging has revolutionized the study of the organization of the human brain and how its structure and function are altered in psychiatric disorders. A critical explanatory gap lies in our mechanistic understanding of how systems-level neuroimaging biomarkers emerge from underlying synaptic-level perturbations associated with a disease state. I will present an emerging “computational psychiatry” approach that leverages biophysically-based computational models of large-scale brain activity, grounded in dynamical systems theory, and their potential integration with clinical and pharmacological neuroimaging. In particular, I will focus on circuit models which describe how patterns of correlated spontaneous neural dynamics (i.e., functional connectivity) are shaped by long-range synaptic interactions. These simulated signals can be related to experimental neuroimaging measurements in human subjects, such as resting-state functional MRI, to fit model parameters. Model parameters are biologically interpretable and represent processes implicated in psychiatric disorders, including the synaptic balance of excitation and inhibition in cortical microcircuits, local vs. global coupling strengths, and neuronal noise. Our recent research highlight the importance of local circuit physiological dynamics, in combination with structural connectivity, in shaping the emergent functional connectivity. Furthermore, heterogeneity of local circuit properties across brain areas, which impacts large-scale dynamics, may be critical for modeling whole-brain phenomena and alterations in psychiatric disorders and pharmacological manipulation.

# Normalization of periodic delays in delay differential equations arising from population dynamics

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We consider the scalar delay differential equation with time-varying delay,

$$x'(t) = f(t, x(t), x(t - \tau(t))).$$

The equation captures the dynamics of a single species population such as ticks, when the lag function  $\tau(t)$  is a periodic function. We consider the possibility of transforming the equation to a delay differential equation with a constant delay.

## Learning PDE models from noisy spatiotemporal data

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We consider the problem of learning the dynamics governing a given noisy dataset using sparse regression methods. Recent studies in this area have only been successful in the presence of very small amounts of noise. We accordingly develop a method to denoise noisy data for use in an equation learning framework and demonstrate that this method can correctly identify the PDE model that generated noisy spatiotemporal data. This work is a first step towards developing a methodology to generate data-driven PDE models from biological data.

**Limited processivity of single motors improves overall transport flux of self-assembled  
motor-cargo complexes**

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I will propose a new mechanism for how limiting processivity of single motors can enhance cargo transport on the cellular scale.

## Prevalence of deficiency zero reaction networks

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In the mathematical study of reaction networks, the most classical results are those pertaining to models that have a deficiency of zero. In particular, for deterministic models it is well known that weak reversibility and a deficiency zero of the reaction network implies that the model is complex balanced. In the stochastic setting it is known that weak reversibility and a deficiency of zero implies the existence of a stationary distribution that is a product of Poissons.

Given that deficiency zero models play such a significant role in the mathematical study of reaction networks, a natural question is how prevalent are they? In order to answer this question, we consider reaction networks under the Erdos-Renyi random graph framework. In particular, we start with  $n$  species, and then let our possible vertices be all zeroth, first, and second order complexes that can be produced from the  $n$  species. Edges, or reactions, between two arbitrary complexes then occur independently with probability  $p_n$ . We establish a function  $r(n)$ , termed a *threshold function*, such that the probability of the random network being deficiency zero converges to 0 if  $p_n \gg r(n)$  and converges to 1 if  $p_n \ll r(n)$ .

## Using Oscillations to Encode Information in the Hippocampus

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The hippocampus is capable of rapidly learning incoming information, even if that information is only observed once. Further, this information can be replayed in a compressed format in either forward or reversed modes during Sharp Wave Ripples (SPW-R's). In this work, we demonstrate how networks acting as distinct oscillators can facilitate single-trial learning of information by acting as nearly orthogonal temporal bases. By using an interference of oscillators mechanism, the temporal basis created by these oscillators becomes compressible, allowing for compressible learning, as seen during SPW-R's. Finally, due to the near, but not perfect orthogonality of these systems, dynamical signatures that learning has occurred emerge in the network. For a temporal basis created by interfering oscillators, nested, higher frequency assembly segregation emerges due to learning.

## Machine learning combined to mechanistic modeling of differential effects of neo-adjuvant Sunitinib on primary tumor and metastatic growth

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Angiogenesis inhibitors have proved to hinder established tumor growth in several studies. However, recent experimental evidence also suggests limited efficacies of these drugs in preventing metastatic spread.

We extended a mathematical metastatic model to describe primary tumor and metastatic dynamics in response to neo-adjuvant sunitinib in a clinically relevant mouse model of spontaneous metastatic breast cancer. The experimental data comprised longitudinal measurements of primary tumor size and metastatic burden in a total 104 mice over multiple scheduling groups, as well as survival data and pre-surgical biomarkers (circulating tumor cells and myeloid-derived suppressor cells counts and proliferation and endothelial immunohistochemical markers). A non-linear mixed effects modeling approach was used to quantify inter-animal variabilities in metastatic dynamics and survival, and machine learning algorithms were applied to investigate the significance of the biomarkers as predictors of individual dynamics.

Model simulations considering the effect of treatment on primary tumor growth only described well the experimental data of all the treated groups, suggesting limited effect on metastatic growth. Interanimal variability was mainly characterized by a model parameter  $\mu$  expressing the metastatic potential of the tumor, which was also found to be significant for predicting survival. However, the biomarkers included in all tested machine learning algorithms (including support vector machines, random forests and artificial neural networks) demonstrated only limited predictive power on the mathematical parameters ( $R^2 = 0.13 - 0.2$ , best relative error on  $\ln(\mu)$  9.83 ± 10.70 %).

The mathematical model developed represents a basis for testing new combination regimens in the design of preclinical studies and paves the way to the combination of artificial intelligence techniques with mechanistic modeling in personalized oncology.

## Demographic Variability, Environmental Variability, and Periodic Fluctuations in Stochastic Epidemic Models with Two Patches

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Seasonality and contact patterns due to environmental fluctuations, social behavior, and physical proximity affect the dynamics of disease outbreaks. Recent studies applied to deterministic and stochastic epidemic models with periodic environments have shown that the average basic reproduction number is not sufficient to predict whether an outbreak occurs. We extend these studies to continuous-time, nonhomogeneous stochastic epidemic models with demographic variability, environmental variability, and periodicity to investigate the combined effect of periodicity and variability on disease dynamics for a stochastic epidemic model, where disease is spread between two regions or patches. The continuous-time nonhomogeneous stochastic processes have either discrete or continuous random variables. A multitype branching process approximation is used to calculate the probability of a disease outbreak with demographic variability and periodicity. A numerical study of the dynamics of stochastic patch models with environmental variability and periodicity are investigated in terms of probability of a disease outbreak and the dynamics near an endemic state. The implications of these results for disease control are also discussed.

## Rescorla Wagner Models with Dynamic Attention

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The Rescorla-Wagner model (RW) is frequently used to model human learning of cue-response associations because it balances the tradeoffs between limited memory and limited processing. RW proposes that an agent learns the associations between cues and subsequent responses by dynamically updating cue association weights proportionally to a prediction error. While this model has proven informative in controlled human experiments with a small number of cues, it is widely suspected that this model can not scale to a large number of cues and noisier environments, both of which reflect everyday life. Indeed, we conclusively demonstrate the scaling problems of RW on a simple ‘needle in a haystack’ problem. Instead, recent work suggests that humans modulate their attention to focus on the most predictive cues while ignoring uninformative cues. RW with dynamic attention not only satisfies a constraint on human attention bandwidth, it better describes experimental human data, and, as we show, also performs better on a number of natural learning tasks. However, given the fundamental difficulties involved in feature selection, dynamic attention faces numerous additional difficulties beyond those faced by RW. We demonstrate several ways in which dynamic attention can fail, explain those failures and leverage that understanding to produce a new weighted centered dynamic attention RW model that overcomes these problems. Given the simplicity of these alterations and their effects we hope that future computational psychiatry practitioners will explore similar modifications to their online learning benchmarks.

## Impact of temperature and diurnal temperature range on the transmission dynamics of malaria

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Malaria is mainly a tropical disease and its transmission cycle is heavily influenced by environmental climate condition. In particular, temperature strongly affects the life-cycle of the *Anopheles* mosquito vector and *Plasmodium* parasite, while rainfall is necessary for the existence of suitable aquatic habitat for the development of immature mosquito. This talk will introduce a novel weather-driven deterministic model for the transmission dynamics of malaria. The model incorporate several epidemiological features of both humans and mosquitoes in malaria transmission dynamics such as, the gonotrophic cycle of the *Anopheles* mosquitoes, the *Plasmodium* sporogonic cycle as well as transmission from asymptotically infected humans. Results from the analysis of the model show that malaria burden varies nonlinearly with temperature. In addition, the results obtained suggest that, when the reproduction number of the model ( $\mathcal{R}_0$ ) is relatively small, changes in model parameter values may significantly affect the burden of malaria, however, when the baseline  $\mathcal{R}_0$  is significantly high, disease burden is insensitive to such change. Furthermore, this study show that increasing diurnal temperature range (DTR) shifts the optimal temperature for maximum malaria transmission from 29°C (when DTR is 0°C) to 25°C (when DTR is 15°C).

## Combinatorics of Reaction Networks with Complex Balance

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This work explores the combinatorics of stochastic chemical reaction networks (SCRN) that satisfy a complex balance property. The idea consists of reinterpreting the probability generating function of SCRN as a combinatorial generating function. Doing so casts the probability distribution of an SCRN as a combinatorial species. We describe the various structures that result from the combinatorial interpretation of SCRN. In particular, we find combinatorial interpretations of the dynamics and stationary behavior of SCRN, and we specialize the latter to the case of systems that satisfy a complex balance property. In this case, the stationary behavior simplifies significantly and its combinatorial generating function takes the form of an exponential of molecular species, which is simply interpreted as the combinatorial class of multisets of species weighted by their energy. A change of variables allows us to obtain the generating function of factorial moments of SCRN. We provide the combinatorial interpretation of factorial moments as well as an analytical formula for the moment hierarchy of systems with complex balance. Finally, we present methods for approximating the coefficients of generating functions, which are necessary for explicit calculations of probabilities and moments.

## Speed determinacy of traveling waves to the Lotka-Volterra competition model

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**ABSTRACT:** In this talk, the minimal-speed determinacy of traveling wave fronts of a two-species competition model of diffusive Lotka-Volterra type is investigated. First, a cooperative system is obtained from the classical Lotka-Volterra competition model. Then, we apply the upper-lower solution technique on the cooperative system to study the traveling waves as well as its minimal-speed selection mechanisms: linear or nonlinear. New types of upper and lower solutions are established. Previous results for the linear speed selection are extended, and novel results on both linear and nonlinear selections are derived. This is a joint work with Dr. Ahmad Alhasanat.

## Influence of Preventative Measures on the Spread of the Zika Virus

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The Zika arbovirus transmitted by the Aedes aegypti mosquitoes has been shown to be capable of infecting humans via two routes: the bites of infected vectors and through sexual contacts involving infected and non-infected persons. There is no treatment or current prevention and mitigating efforts rely on the use of the Centers for Disease Control and Prevention recommendations including the use of insecticide-treated bed nets (ITN) and indoor residual spraying (IRS). In this work, we investigate via a mathematical model, the role of ITN and IRS as methods for limiting the impact of Zika transmission. We introduce a model that builds on classical SEIR epidemiological single outbreak models. We compute the basic and control reproduction numbers and the final epidemic size in the presence of control measures ITN and IRS. We derive a gross estimate for the rate of sexual transmission, during the initial stages of the outbreak, in terms of prior estimates of the basic reproduction number from related albeit not sexually transmitted arboviral diseases.

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**Presenter:** Peter PANG

**Title:** A cancer invasion model involving chemotaxis and haptotaxis

**Abstract:** In this talk, we will consider a cancer invasion model involving chemotaxis and haptotaxis in two spatial dimensions. This model involves two parabolic PDEs and an ODE. The novelty of this study lies in: first, our treatment of the full parabolic model (whereas previous studies simplify one PDE to its elliptic version), and second, allowing for self-remodeling of the extracellular matrix (whereas previous studies normally assume its absence). The presence of the ODE presents particular mathematical challenges with regard to regularity. Under appropriate regularity assumptions on the initial data, by using adapted  $L^p$  estimate techniques, we are able to establish global existence and uniqueness of classical solutions in the high cell proliferation regime.

**Subdiscipline:** Mathematical oncology

## Entropy Production and Cytoskeletal Avalanches in Actin Networks

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Cells constantly utilize non-equilibrium chemical processes to generate a directed response to specific biochemical cues. These responses are largely mediated by the cellular cytoskeleton, which endues cells with their instantaneous shapes, providing a machinery for cells to move around, generate forces and also integrate both chemical and mechanical signaling. Towards uncovering fundamental molecular principles behind cytoskeleton's formation and dynamics, we have developed a unique reactive mechanochemical force-field and software, called MEDYAN (Mechanochemical Dynamics of Active Networks: <http://medyan.org>). MEDYAN integrates dynamics of multiple mutually interacting phases: 1) a spatially resolved solution phase is treated using a reaction-diffusion master equation; 2) a polymeric gel phase is both chemically reactive and also undergoes complex mechanical deformations; 3) flexible membrane boundaries interact mechanically and chemically with both solution and gel phases. We also devised an algorithm for quantifying dissipation in cytoskeletal dynamics, finding that simulation trajectories of entropy production provide deep insights into structural evolution and self-organization of actin networks, uncovering earthquake-like processes of gradual stress accumulation followed by sudden rupture and subsequent network remodeling.

# Impact of adaptive myelination on synchrony in coupled oscillator networks

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White matter pathways form a complex network of myelinated axons that facilitate the transmission of signals in the nervous system, playing a key role in behaviour and cognition. Recent evidence reveals that white matter networks are responsive and adaptive to ongoing brain activity and function, as opposed to having a fixed structure. Consequently, the temporal distribution of conduction delays is continuously adjusting in order to regulate spike-time arrivals and synchrony among various brain areas. This plasticity mechanism has yet to be widely considered in computational neural models, with conduction delays being constant over time or ignored altogether. As a prototype, we modify a canonical Kuramoto oscillator model by equipping all connections with plastic, phase-dependent delays. In large-dimensional, distributional settings, mathematical and numerical analysis demonstrates that such evolving delays act as a stabilizing mechanism that promotes the network's ability to maintain synchronous outputs. Specifically, our work shows that global synchronization is more resilient whenever conduction delays can adapt, in particular to damages sustained in network architecture through injury. Our results highlight the importance of incorporating activity-dependent myelination into the context of computational models.

## Scalar Reduction of a Neural Field Model with Spike Frequency Adaptation

Youngmin Park (presenter)<sup>a</sup> and Bard Ermentrout<sup>b</sup>

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We study a deterministic version of a one- and two-dimensional attractor neural network model of hippocampal activity first studied by Itskov et al 2011. We analyze the dynamics of the system on the ring and torus domain with an even periodized weight matrix, assuming weak and slow spike frequency adaptation and a weak stationary input current. On these domains, we find transitions from spatially localized stationary solutions (“bumps”) to (periodically modulated) solutions (“sloshers”), as well as constant and non-constant velocity traveling bumps depending on the relative strength of external input current and adaptation. The weak and slow adaptation allows for a reduction of the system from a distributed partial integro-differential equation to a system of scalar Volterra integro-differential equations describing the movement of the centroid of the bump solution. Using this reduction, we show that on both domains, sloshing solutions arise through an Andronov-Hopf bifurcation and derive a normal form for the Hopf bifurcation on the ring. We also show existence and stability of constant velocity solutions on both domains using Evans functions. In contrast to existing studies, we assume a general weight matrix of Mexican-hat type in addition to a smooth firing rate function.

## Multiple Dose Pharmacokinetic Models Predict Bioavailability of Toxins in Vertebrate Herbivores

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A compartmental pharmacokinetic model is built to predict the concentration of toxic phytochemical in the gastrointestinal tract and blood following orally intake by an individual vertebrate herbivore. The existing single and multiple dose pharmacokinetic models are extended to incorporate the physiological factor that toxins can be excreted unchanged in feces due to gastrointestinal motility by impulsive differential equations. An index is defined to be the fraction of the toxin in the blood (i.e., bioavailability) attributed to the excretion effect. Sensitivity analysis is conducted and it is found that for any toxin, the coefficient of bioavailability which is attributed to the elimination effect of gastrointestinal motility depends mostly on absorption rate of toxin from GIT into the blood, frequency of elimination due to gastrointestinal motility, and the frequency of toxin intake.

## Compensatory foraging in stoichiometric producer-grazer models

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Nutritional constraints are common as food resources are rarely optimally suited for grazing species. Elemental mismatches between trophic levels can influence population growth and foraging behaviors. Grazing species, such as *Daphnia*, utilize optimal foraging techniques, such as compensatory feeding. Here we develop two stoichiometric producer-grazer models, a base model that incorporates a fixed energetic foraging cost and an optimal foraging model where energetic foraging costs depend on food nutritional content. A variable energetic foraging cost results in cell quota dependent predation behaviors. Analyzing and comparing these two models allows us to investigate the potential benefits of stoichiometric compensatory foraging behaviors on grazer populations.

## Islet Network Analysis: Determining Conditions for Behaviors Related to Silencing “Hub” Cells

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Insulin producing beta cells are coupled within a functional syncytium called an islet of Langerhans. Heterogeneity within this syncytium can lead to glucose-induced initiation of activity at one or multiple loci, activity that tends to organize due to the electrical coupling of neighboring cells. Recent experimental work suggests certain “hub” cells may consistently act as such locus cells and can be defined by functional connectivity interpreted as correlated calcium traces. Silencing hub cells has been shown to be able to suppress entire islet activity. Here we attempt to categorize this behavior according to several characteristics, including scale-free network, de/synchronization measures, silencing of hub cells via pseudo-optogenetics, and we apply a network model framework including coupling strength and cellular excitability to test these conditions. We find that with moderate coupling silencing identified hub cells is insufficient to silence network activity, however several conditions can be manipulated to nearly reproduce some of the effects. Some of the conditions include a) threshold of surrounding cells is very near threshold but not self-oscillatory, b) the hub cell is sufficiently active, c) significant noise is added, d) coupling is reduced, and e) special geometry is considered. The fragility of the hub cell structure calls into question the robustness of this hypothesis.

## Multi-scale time-since-infection models in evolutionary epidemiology

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The study of evolutionary epidemiology is vital to understand and control the spread of anti-microbial resistance, but is inherently challenging because pathogen evolution is driven by forces acting at multiple scales: for example, HIV needs to escape the immune system within a host, but also needs to maintain the ability to be transmitted efficiently between hosts. I will argue that time-since-infection models are much more flexible than ODEs if we want to allow for realistic enough aspects of both within- and between-host scales, but that capturing the feedback loops between such scales is a formidable challenge.

Using HIV as an example, I will discuss current models and their limitations, with particular attention to the implications of the fundamental structural assumptions on models' behaviour. Furthermore, I will discuss the main technical challenges I see in developing a general theory for time-since-infection models that allow for superinfection (e.g. multi-strain systems with partial cross-immunity), starting from the problem of characterising the system's steady states.

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Title: Does the Ecology of Somatic Tissue Normally Constrain the Evolution of Cancer?

Resource ecology typically constrains and guides evolution, and the somatic cellular evolution of cancer may be no exception to this. Several major risk factors for cancer involve vascular oversupply of energy to affected tissues. Here, we propose a potential mechanistic explanation for the association between energy oversupply and cancer risk, which we call the metabolic cancer suppression hypothesis: We hypothesize that oncogenesis is normally suppressed by organismal physiology that regulates and strictly limits normal energy supply to somatic cells, and that this protection is removed by abnormal oversupply of energy.

We evaluate this hypothesis using a computational model of somatic cell evolution to simulate experimental manipulation of the vascular energy supply to a tissue. The model simulates the evolutionary dynamics of somatic cells during oncogenesis.

In our simulation experiment, we found that under plausible assumptions, elevated energy supply to a tissue led to the evolution of elevated energy uptake by somatic cells, leading to the rapid evolution of both defining traits of cancer cells: hyperproliferation, and tissue invasion.

Our results support the hypothesis of metabolic cancer suppression, suggesting that vascular oversupply of energetic resources to somatic cells removes normal energetic limitations on cell proliferation, and that this accelerates cellular evolution toward cancer.

## Regulation of T cell expansion by antigen

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An essential feature of the adaptive immune system is the proliferation of antigen-specific lymphocytes during an immune response. This proliferation must be regulated to ensure an effective response while avoiding immunopathology. Recent experiments in mice have demonstrated that the expansion of an antigen-specific clone of T cells in response to cognate antigen obeys a striking inverse power law with respect to the initial number of T cells. Here, we show that such a relationship arises naturally from a model in which T cell expansion is limited by decaying levels of presented antigen. The same model also accounts for the observed dependence of T cell expansion on affinity for antigen and on the kinetics of antigen administration. Using the model to derive optimal vaccination protocols, we find that exponentially increasing antigen doses can achieve a nearly optimized response. Our model suggests that the dynamics of presented antigen is a key regulator of the adaptive immune response.

# A stochastic dynamical systems approach to understand cell fate transitions during embryonic development

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Traditional descriptions of cellular states involve static pictures of gene expression. Nevertheless, during embryo development cells are under constant transformation, challenging this static view, and requiring tools that provide a quantitative description of the timing and nature of these transients. In this talk I will discuss how stochastic dynamical systems can be applied to address this problem in particular by using minimum action path theory in different scenarios with different dynamical properties and dimensionality. In particular I will show how we can use this framework to understand the patterning of the neural tube in response to a morphogen gradient, and how we can obtain the details of the exit dynamics out of a stable oscillatory cellular state.

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PLOS Computational Biology (Accepted) (2019)

## Microtubule cytoskeleton self-organisation in cells with anisotropic cytoplasm

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Most of the current models of microtubule dynamics assume that the underlying medium is isotropic. However, the cell cytoplasm is highly anisotropic due to the presence of mitochondria and actin filaments, etc. These barriers for microtubule growth and the background flow created by movement of motor proteins inside the cell, strongly affect microtubule self-organisation.

We develop an analytical and numerical models of microtubule self-organisation in anisotropic cytoplasm, and apply it to the example, where anisotropy arises due to the actin cable, from which we can deduce the experimental catastrophe rates of microtubule upon reaching the actin cables. One aspect critical to the efficacy is the microtubule bundling factor - the parameter that measures which fraction of microtubules are in antiparallel bundles. We will show how the bundling factor depends on the anisotropy of the microtubule cytoskeleton self-organisation and briefly address its effects on the intracellular transport.

## Dynamics of a childhood disease model with isolation

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Epidemiological models with exponentially distributed disease stages, although simpler to analyze, have been shown to have limitations in many cases. The model results can be improved by considering more realistic distributions. In this talk, I will present a model with gamma distributions for the exposed and infectious stages to study the impact of isolation on sustained oscillations observed in many childhood diseases. This model is an extension of the model considered in Feng and Thieme (Math Biosc. 1994), in which exponential distributions are assumed for disease stages and it is shown that the threshold value for isolation to generate sustained oscillations is very long for most childhood diseases. By analyzing the stability of the endemic equilibrium and the threshold for Hopf bifurcation of our model, we show that the minimum value for the isolation period required for Hopf bifurcation can be reduced significantly so that the model can be applicable to many childhood diseases.

## Model Reduction for a Stochastic Evolutionary Game Model

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In a stochastic evolutionary game the species relative fitnesses guides the evolutionary dynamics with fluctuations due to random drift. A selection advantage which depends on a changing environment will introduce additional possibilities for the dynamics. We analyse a simple model in which a random environment allows competing species to coexist for a long time before a fixation of a single species happens. In our analysis we use stability in a linear combination of competing species to approximate the stochastic dynamics of the system by a diffusion on a one dimensional co-existence region. Our method significantly simplifies calculating the probability of first extinction and its expected time, and demonstrates a rigorous model reduction technique for evaluating quasi-stationary properties of stochastic evolutionary dynamics.

## Deciphering the transport of intermediate filaments by motor proteins

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Intermediate filaments are elastic fibres that are transported in cells by microtubule-associated motor proteins kinesin and dynein. How elastic filaments are efficiently transported by antagonistic motors is not well understood and difficult to measure with current experimental techniques. Adapting the tug-of-war paradigm for vesicle-like cargos, we develop a mathematical model to study the motion of an elastic filament punctually bound to antagonistic motors. As observed in cells, up to 3 modes of transport are obtained; dynein-driven retrograde, kinesin-driven anterograde fast motions and a slow motion.

Motor properties and initial conditions, which depend on intracellular context, regulate the transport of filaments. Furthermore, the mechanical and biochemical properties of filaments are found to regulate their mode of motion. Filaments elasticity is found to affect both the mode and the efficiency of transport. We further show that the coordination of motors along the filament emerges from the interplay between intracellular context and elastic properties of filaments.

## Multiscale Modelling of Cancer: Towards Predicting Multimodality Treatment Outcomes

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Cancer involves complexities in multiple spatio-temporal scales and currently, there exists a wide range of mathematical models with varying complexities, capturing different aspects of tumour behaviour. Here, we use a validated hybrid individual cell-based mathematical and computational model, incorporating single-cell based intracellular dynamics, the cell microenvironment and cell-cell interactions to study the growth, progression and treatment responses of cancer cell mass. In particular, this multiscale approach is used to investigate the effects of combination therapy with Hypoxia Activated Prodrugs (HAPs) and radiation.

Tumour hypoxia has been associated with therapy resistance of multiple cancer treatments and in particular, radiation therapy. HAPs are bioreductive prodrugs that target hypoxic area and remain inactive, until activated under the presence of hypoxia. Despite being conceptually promising, clinical trials involving HAPs have produced mixed outcomes. Our initial results indicate that the effectiveness of HAP in enhancing radiation damage depends on multiple factors such as tumour oxygenation status (spatial and temporal) and bystander responses of cells to HAPs.

## Invasion speeds in highly variable landscapes: multiple scales, homogenization and the migration of trees

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We use multiscale techniques and the method of homogenization to explore the behavior of invasion waves in highly variable landscapes. Many tree species, in particular the Southwestern pinyon pines and junipers, are dispersed by frugivorous birds (e.g. robins, jays and cedar waxwings). Rates of spread for plant species are conditioned on dispersal distances and probabilities of germination/establishment. However, direct observation of seed position after dispersal is difficult due to landscape heterogeneity and the scale of dispersal, but behavioral time budgets for dispersers in various habitats are readily available. Likewise, rates of germination and establishment vary markedly from patch to patch in a landscape. To complicate things further, habitat type effects on seed fate and disperser behavior are highly correlated. In the limit of highly variable landscapes, we use homogenization to derive closed-form dispersal kernels for seed dispersal which can be parameterized from disperser time budgets. Further asymptotic analysis allows us to predict the migration speed of tree species in heterogeneous landscapes, even when seed fate is highly correlated with habitat type. Predictions are compared with prehistoric migration estimates of pinyon pine and juniper in southern Utah.

## Stochastic Shielding Analysis of Conductance-Based Neuron Models Under Current Clamp

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In many neural systems, random gating of ion channels is a significant source of dynamical variability. Numerical simulation methods based on Markov Chain (MC) representations are recognized as the most accurate methods, however, their computational cost becomes too expensive for large numbers of channels. Previous studies have proposed a variety of stochastic differential equation models, particularly Langevin models, as approximations of an underlying MC. At the same time, Schmandt and Galán (2012) introduced the stochastic shielding (SS) approximation as a fast, accurate method for approximating the Markov process using only a subset of the observable state-state transitions. Unlike more traditional state-aggregation techniques, SS reduces the dimension of the stochastic process in the *sample space* by eliminating those independent noise sources that have the least impact on current fluctuations.

In this talk, we describe how to combine the stochastic shielding approximation with Langevin simulations of the Hodgkin-Huxley model. Specifically, we derive analytic results for the decomposition of the variance of the stationary interspike interval (ISI) distribution into contributions from specific state transitions for the sodium and potassium ion channels. Our theory is exact in the limit of small channel noise; through numerical simulations we demonstrate its applicability over a range of noise levels. Importantly, our results apply to *current clamp* rather than voltage clamp conditions. Under current clamp, a stochastic conductance-based model is an example of a piecewise-deterministic Markov process (PDMP), and our analysis is the first to provide a resolution of macroscopic timing variability in terms of molecular-level fluctuations for such a process, to the best of our knowledge. Our analysis quantifies the relative contributions of individual ion channel state transitions to ISI variability, and shows that the edges making the largest contribution to current fluctuations under voltage clamp do not necessarily coincide with those making the greatest contribution to ISI variance under current clamp.

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## Idealized Models of Insect Olfaction

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When a locust detects an odor, the stimulus triggers a specific sequence of network dynamics of the neurons in its antennal lobe, characterized by synchronous oscillations, followed by a short quiescent period, with a transition to slow patterning of the neuronal firing rates, before the system finally returns to a background level of activity. We model this behavior using an integrate-and-fire neuronal network, composed of excitatory and inhibitory neurons, each of which has fast-excitatory, and fast- and slow-inhibitory conductance responses. We further derive a firing rate model for the excitatory and inhibitory neuronal populations, which allows for more detailed analysis of and insight into the plausible olfaction mechanisms seen in experiments, prior models, and our numerical model. We formulate two mathematical models to describe the possible underlying mechanisms by which insects detect and identify odors using a coarse-grained approach. The resulting firing rate model incorporates the slow and fast conductance timescales believed to play a vital role in the network behavior of the locust antennal lobe. The fast dynamics arise as an attracting limit cycle, followed by a pause in activity due to the slow variable, before a much slower oscillatory pattern reemerges.

## Traveling Wave of Some Reaction-Diffusion Systems, Results and Open Questions

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**Abstract:** In this talk, I shall report some recent progress on the existence and multiplicity of traveling waves to some reaction-diffusion systems which include Gray-Scott system as well as Lotka-Volterra competition system.

In addition, I shall pose some open questions which are interesting and challenge, demanding new ideas and fresh approaches.

This is a joint-work with Xinfu Chen and Guirong Liu.

## A network model of the striatum captures hyperactivity patterns in obsessive compulsive disorder

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The neuronal circuit that controls the execution of stereotyped behaviors, like stretching our arms when we wake up in the morning or washing our hands, involves three major regions of the brain: the cortex, the striatum and the thalamus. Taken together, these regions compose the cortico-striatal-thalamo-cortical (CSTC) pathway. Signal propagation within the CSTC pathway relies on the coordinated activity of long-range projecting excitatory (E) and local inhibitory (I) neurons. Coordinated activation of two types of cells in the striatum (the D1R- and D2R-MSNs), is thought to be crucial for movement execution. There is currently no clear understanding of the basic mechanisms that generate hyperactivity within the CSTC pathway, which has been observed in patients with increased motor activity, like the ones affected by obsessive compulsive disorder (OCD). We have been working on a mathematical framework addressing *how the balance of E/I onto D1R- and D2R-MSNs affects execution of motor tasks and information transfer within the CSTC pathway.*

In a preliminary model, which will be presented briefly, we investigated the effects of altering the E/I bias in a simplified system (each CSTC functional area acting as a homogeneous unit, with activity captured by one variable). For this model of coupled nonlinear components, we quantified the excitatory and inhibitory elements of the feedback loop, and analyzed their effects over time and under perturbation. Using a bifurcation analysis, we established how different types of E/I imbalance may lead to phase transitions of the system into a regime of steady hyperactivity, or of oscillations in and out of hyperactivity (both regimes expected to appear within the OCD functional range). In reality, however, each of our modeled variables is a network of neurons, some of which are synchronized, but which in general may have distinct patterns of activity. In our current iterate of the model, we are working on combining two spatio-temporal scales: a physiological one (in which D1 and D2 striatum sites are modeled as networks of single Hodgki-Huxley neurons), and a functional one (the other network nodes are represented at a mean field, population activity scale). We present our modeling techniques of reconciling these two aspects, as well as results that reflect how the system's behavior (interpreted now at both scales) depends on the E/I balance and on the striatum network architecture.

## How do immune cells kill cancer cells?

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The immune system is able to fight cancer by mustering and training an army of effector “killer” cells. There are several key steps to this process: recognition of the cancer cells, activating the effector cells, trafficking of the immune cells to the site of the tumor, and the killing itself. We have created a cell-based fixed-lattice model that simulates immune cell and tumor cell interaction involving MHC recognition, and two killing mechanisms.

We are motivated by open questions about the mechanisms behind experimentally observed kill rates of tumor cells by different types of effector cells. These mechanisms play a big role in the effectiveness of many cancer immunotherapies. Results from model simulations, along with theories developed by ecologists, can help to illuminate which mechanisms are at work in different conditions.

## TimeTeller: a New Tool for Precision Circadian Medicine and Cancer Prognosis

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I will present a machine-learning approach to measuring circadian clock functionality from the expression levels of key genes in a single tissue sample. A principal aim of circadian medicine is to develop techniques and methods to integrate the relevance of biological time into clinical practice. However, it is difficult to monitor the functional state of the circadian clock and its downstream targets in humans. Consequently, there is a critical need for tools to do this that are practical in a clinical context and our approach tackles this. We apply our algorithm to breast cancer and show that in a large cohort of patients with non-metastatic breast cancer the resulting dysfunction metric is a prognostic factor for survival providing evidence that it is independent of other known factors. While previous work in this area is focused on individual genes, our approach directly assesses the systemic functionality of a key regulatory system, the circadian clock, from one sample.

## Steady-state stability in diseases with diffusion

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In many human diseases, including cholera and rabies, the diffusivity properties of the various compartments may vary. In this work, we focus on situations where the mathematical model contains one diffusing compartment (PDE) that is coupled with other compartments that are modeled by ODEs. When studying the linear stability of steady states, one ends up with rational eigenvalue problems. The difficulty with these problems, from the point of view of both analysis and numerical experimentation, is that one has no apriori information as to where the spectrum of the problem might lie. Here, we show that a number of the properties of self-adjoint eigenvalue problems (including the reality of the spectrum) carry over to the operators considered in this work. Our analysis is based on the theory of Herglotz functions.

## PDE modeling simulations and fitting methods for understanding hepatitis B virus infection in humanized mice

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We recently characterized HBV kinetics in blood and liver from the time of inoculation until steady state in mice with humanized livers. We found that immediately after inoculation, the HBV half-life in blood is approximately 1 hour followed by an unexpectedly multiphasic viral amplification in the serum in the absence of adaptive immune response. I will present our ODE and PDE modeling efforts to explain the nature of this observed highly dynamic HBV infection.

## Survival Dynamical Systems on Random Graphs

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The idea of a survival dynamical system (SDS) is to apply aggregated dynamics of a macro model at the level of an individual agent. SDS may be also viewed a limit of agents' dynamics obtained when replacing individual's random hazard function with its large volume limit. Under this second interpretation it is relatively simple to obtain an extension of the classical mass-action SDS to a configuration model random graph and to provide some basic results allowing for estimating the underlying epidemic parameters from micro-level data. As it turns out, in a certain class of degree distributions the SDS model takes a particularly simple form and its statistical analysis is only moderately more complicated than the classical mass-action SDS as given by standard SIR equations.

# A proof of unlimited multistability for phosphorylation cycles

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Information is stored in cells by the phosphorylation of proteins. A simple example of this process is the multiple futile cycle, where a single protein is phosphorylated at  $n$  different sites according to certain rules. This situation can be modelled by a set of  $3n + 3$  ordinary differential equations. To understand the capacity of the system for information storage it is important to know how many steady states there can be. Let  $M(n)$  be the largest integer smaller than  $\frac{n}{2}$ . A decade ago it was proved that there are parameters for which the multiple futile cycle has at least  $2M(n) + 1$  steady states. More interesting for the biology is the question of how many *stable* states there are. Recently we proved that there are parameters for which the multiple futile cycle has at least  $M(n) + 1$  stable steady states. To do this the problem for the ODE describing the multiple futile cycle was reduced by a timescale separation to the corresponding problem for a Michaelis-Menten system of  $n + 1$  ODE. In the latter system the steady states were produced in a single bifurcation, where the centre manifold of the bifurcation point is of dimension one. In this way the analytical problem could be reduced to an algebraic one. It remained to study the eigenvalues of certain matrices and to do a perturbation expansion for the dynamics on the centre manifold. This analysis exhibits a method by which the study of multistationarity in biochemical reaction networks (about which there is an extensive literature) can be extended to understand the question of multistability.

## Mechanical and chemical signaling in single and collective cell migration

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Single and collective cell migration involves both chemical and mechanical signaling between cells and the extracellular matrix (ECM, a fibrous network surrounding cells). Adhesive forces between cells and physical stresses from the ECM allow cells to coordinate their behavior with neighbouring cells. Regulatory proteins (Rho GTPases) coordinate cell shape changes and migration. We developed a cellular Potts model (CPM) that incorporates wave-pinning dynamics of Rho GTPase in the cell, by solving PDEs in the deforming cell. We assume that the active level of Rho promotes cell contractions. As a result, the cell exhibits polarized movement. Interestingly, two polarized cells initially move together but then start to swirl around each other. My next step is to study how feedback between Rho GTPases and physical forces affects cell migration. Rho GTPases are upregulated under force and in turn higher GTPase levels are associated with higher cell traction forces. I will discuss how such dynamics may be included into a previously developed multiscale model that includes cell traction forces and ECM stresses. Here, I will also briefly discuss our recent algorithm that derives force fields from the CPM and allows us to track forces and cell behavior. Finally, I will show some preliminary results of the mechanochemical feedback in cell migration along a chemical gradient. In conclusion, our model may shed light on how interactions between forces and signaling can drive single and collective cell migration.

## Analysis of an innate immune response model and the role of inflammation in atherosclerosis

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Macrophages can be activated to a more inflammatory M1 phenotype or to an M2-like phenotype, which promotes the resolution of inflammation. Problems with this phenotypic switching of pro-inflammatory M1 macrophages to an M2 phenotype is essential from appropriate resolution of inflammation can result in a population imbalance that leads to chronic wounds or disease. We have developed a model for the sequential influx of immune cells in the peritoneal cavity in response to a bacterial stimulus that includes macrophage polarization. With this model we are able to reproduce the expected timing of sequential influx of immune cells and mediators in a general inflammatory setting. Sensitivity analysis and numerical simulations were used to explore which dynamics give rise to changes in outcome. This model is the core framework for a model of plaque formation in atherosclerosis. Atherosclerotic cardiovascular disease is a leading cause of morbidity and mortality despite significant advances in lipid management. Complex cellular interactions occur within the artery wall requiring the infiltration/egress of immune cells and lipoproteins within a changing inflammatory milieu and lead to the progression of an atherosclerotic plaque. To model we expanded the peritoneal cavity model into A two-compartment model includes local and systemic dynamics. We use this model to look at the connection between systemic and local measures immune cells and pro-and anti-inflammatory mediators.

## Mathematical Modeling of the Immune-Mediated Theory of Metastasis

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Accumulating experimental and clinical evidence suggest that the immune response to cancer is not exclusively *anti-tumor*. Indeed, the *pro-tumor* roles of the immune system — as suppliers of growth and pro-angiogenic factors or defenses against cytotoxic immune attacks, for example — have been long appreciated, but relatively few theoretical works have considered their effects. Inspired by the recently proposed “immune-mediated” theory of metastasis, we develop a mathematical model for tumor-immune interactions in the metastatic setting, which includes both *anti-* and *pro-tumor* immune effects, and the experimentally observed tumor-induced phenotypic plasticity of immune cells (tumor “education” of the immune cells). Upon confrontation of our model to experimental data, we use it to evaluate the implications of the immune-mediated theory of metastasis. We find that tumor education of immune cells may explain the relatively poor performance of immunotherapies, and that many metastatic phenomena, including metastatic blow-up, dormancy, and metastasis to sites of injury, can also be explained by the immune-mediated theory of metastasis. Our results suggest that further work is warranted to fully elucidate the *pro-tumor* effects of the immune system in metastatic cancer.

## Investigating meteorological influences on *Aedes aegypti* and dengue fever

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Dengue fever is a viral disease transmitted by the mosquito species *Aedes aegypti*. Dengue is endemic to many tropical and subtropical regions of the world; however, outbreaks have been occurring in more temperate regions in the last two decades. This emergence of dengue in previously naive populations has been driven by a number of factors including the expansion of the distribution of *Ae. aegypti*, and changes in temperature and precipitation patterns. In particular, temperature and precipitation are known to impact various parts of the dengue transmission cycle, including mosquito development and survival and the incubation period of the virus in the mosquito host, and it is likely that changes in temperature and precipitation patterns have contributed to changes in dengue transmission dynamics. We developed an ordinary differential equations model that expands on the classic vector-host epidemiological models to include time-varying impacts of temperature and precipitation by modeling the impacts of these meteorological phenomena on mosquito development, survival, and virus transmission efficacy. With this model, we explore the relationships between changes in meteorological conditions and *Ae. aegypti* populations and recent outbreaks of dengue in Córdoba, Argentina, a temperate city which has been experiencing dengue emergence since 2009. We utilize the model to investigate the potential role of changes in climate patterns in the emergence of dengue in the city, and we explore the potential consequences of climate change on mosquito population and dengue transmission dynamics. We discuss our model results in the context of their potential implications for mosquito control and dengue mitigation strategies in Córdoba and other temperate cities, including U.S. cities where dengue emergence may be possible.

## Constitutional Dynamic of Prion Assemblies

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The prion paradigm, including the concept of “strain” unifies a number of age-related, devastating neurodegenerative pathologies due to protein misfolding and aggregation in term of pathogenic mechanisms. In essence, host-encoded monomeric proteins are converted into misfolded and aggregated assemblies, which serve as a template for further auto-catalytic recruitment and conversion in the brain. To date, despite important breakthrough in the field, the precise mechanisms of prion replication, host adaptation, and prion mutation with respect to the structural diversity and the dynamics of the prion assemblies remains unknown.

By considering the Prion propagation as a perpetuation and host adaptation of a structural information stored in  $\text{PrP}^{Sc}$  quaternary structure, we explored in the present work the molecular mechanism of structural information transfer by considering the existence of  $\text{PrP}^{Sc}$  subassemblies (referred in the prion literature as prion quasi-species). We prove that infectious prion assemblies are made-up from several  $\text{PrP}^{Sc}$  subspecies that coexist within the same host in a state far from an equilibrium. Through relaxation kinetic measurement, size distribution analysis of  $\text{PrP}^{Sc}$  assemblies during the pathology evolution we prove the existence of a constitutional dynamic network of exchange within different prion subassemblies.

Using various biochemical and biophysical approaches we identified the elementary building block of  $\text{PrP}^{Sc}$  subassemblies (i.e. suPrP) as potential candidate for the vector of exchange. The existence of an exchange network between  $\text{PrP}^{Sc}$  assemblies has two mains physio-pathological consequences. The first is the perpetuation of structural diversity portfolio during prion replication. This structural diversity is at basis of the host adaptation and cross-species phenomenon. The second consequence is the propensity of the exchange network to give an adaptive response to the micro-environment fluctuations.

The introduction of constitutional dynamic concept imported from chemistry to prion paradigm makes prion propagation as a bona fide replication of a network rather than faithful-replication of a structurally deadpan  $\text{PrP}^{Sc}$  assemblies.

Modeling the outbreak and control of African swine fever virus in a large scale pig farm

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The spread of African swine fever virus (ASFV) threatens to reach further parts of China, it may result in devastating economic consequences for the pig farm, especially big scale industry. We focus on the transmission mechanism for virus spread between two units in a big scale farm and estimate the impact of employees on the ASFV transmission. A deterministic model was proposed to simulate transmission dynamics of African swine fever virus (ASFV) in isolated units under various intervention scenarios. The model captures the dynamics of the recent outbreak of ASFV in Jiangsu Province. Our results show that pigs in the farm need a long time to be completely infected, which implies a forced culling to all pigs may not necessary. Moreover, possible control strategies are evaluated through numerical simulations, indicating that simultaneously strengthening disinfection measure and effectiveness of isolation in pig farm would be most effective. The transmission of ASFV in the pig farm can only be controlled when the disinfection rate of feeders reach to 100% together with the feed, materials and pig transport are well controlled.

# Resonance-based mechanisms of generation of oscillations in networks of non-oscillatory neurons

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Several neuron types have been shown to exhibit (subthreshold) membrane potential resonance (MPR), defined as the occurrence of a peak in their voltage amplitude response to oscillatory input currents at a preferred (resonant) frequency. MPR has been investigated both experimentally and theoretically. However, whether MPR is simply an epiphenomenon or it plays a functional role for the generation of neuronal network oscillations, and how the latent time scales present in individual, non-oscillatory cells affect the properties of the oscillatory networks in which they are embedded are open questions. We address these issues by investigating a minimal network model consisting of (i) a non-oscillatory linear resonator (band-pass filter) with 2D dynamics, (ii) a passive cell (low-pass filter) with 1D linear dynamics, and (iii) nonlinear graded synaptic connections (excitatory or inhibitory) with instantaneous dynamics. We demonstrate that (i) the network oscillations crucially depend on the presence of MPR in the resonator, (ii) they are amplified by the network connectivity, (iii) they develop relaxation oscillations for high enough levels of mutual inhibition/excitation, and (iv) the network frequency monotonically depends on the resonators resonant frequency. We explain these phenomena using a reduced adapted version of the classical phase-plane analysis that helps uncovering the type of effective network nonlinearities that contribute to the generation of network oscillations. Our results have direct implications for network models of firing rate type and other biological oscillatory networks (e.g, biochemical, genetic).

# On a Nonlinear Age-structured Model for Tumor Cell Populations with Quiescence

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We present a nonlinear first-order hyperbolic partial differential equation model to describe age-structured tumor cell populations with proliferating and quiescent phases at the avascular stage in vitro. The division rate of the proliferating cells is assumed to be nonlinear due to the limitation of the nutrient and space. The model includes a proportion of newborn cells that enter directly the quiescent phase with age zero. This proportion can reflect the effect of treatment by drugs such as erlotinib. The existence and uniqueness of solutions are established. The local and global stabilities of the trivial steady state are investigated. The existence and local stability of the positive steady state are also analyzed. Numerical simulations are performed to verify the results and to examine the impacts of parameters on the nonlinear dynamics of the model. (Based on a joint paper with Z. Liu, J. Chen, J. Pang and P. Bi)

## Computational modeling of neural stem cell migration routes in the brain

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Neural stem cells (NSCs) are inherently patho-tropic and have been shown to be effective for tissue regeneration and delivery of therapeutics in cases of brain injuries and tumors. The delivery of NSCs in the brain can be either via intracranial, intraventricular or intranasal routes. The therapeutic efficiency of NSCs depends both on the distance between the injection site and target, as well as the route characteristics. Prediction of NSC delivery efficiency and routes of migration based on the injection site is instrumental for optimizing NSC dosage.

We have recently shown the migration of NSCs along white matter in naïve mice brain. Here, we present a computational model for simulation of NSC migration within mice and human brain. Fractional anisotropy atlas of the mouse brain was obtained using Diffusion Tensor Magnetic Resonance Imaging (DT-MRI). The Fiber Assignment with Continuous Tracking (FACT) algorithm which is typically used in tractography, is used to predict migration routes from potential injection sites. The FACT algorithm generates the migration direction based on the direction of dominant eigenvector (from DT-MRI atlas) at the tissue voxel. An injection site was simulated as a specific region from which a number of paths would be stochastically simulated to originate from. Migration paths in mice brain are simulated with potential injection sites in the corpus callosum (CC injection) and olfactory bulb (OB injection).

Results predicted NSC migration routes to be along the corpus callosum and towards the frontal cortex for the CC injection and towards the optic chiasm for the OB injection. The model is applied to human brain DT-MRI atlas to simulate NSC migration paths with putamen as the potential injection site. The model predicts the migration of NSCs to the frontal cortex and along the subventricular zones. The model is well poised to incorporate directed cues for simulation of NSC migration in the presence of tumors or injuries. A successful modeling framework verified against experimental data will be useful for optimizing stem cell therapeutic doses and route of administration on a patient-specific basis.

## Effects of $I_{NaP}$ block in respiratory circuits depend on the pharmacological mechanism

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The mechanism(s) of action of most commonly used pharmacological blockers of voltage-gated ion channels are well understood; however, this knowledge is rarely considered when interpreting experimental data. Effects of blockade are often assumed to be equivalent, regardless of the mechanism of the blocker involved. Using computer simulations and fast-slow decomposition analysis, we demonstrate that this assumption may not always be correct. We simulate the blockade of a persistent sodium current ( $I_{NaP}$ ), proposed to underlie rhythm generation in pre-Bötzingger complex (pre-BötC) respiratory neurons, via two distinct pharmacological mechanisms: (1) pore obstruction mediated by tetrodotoxin and (2) altered inactivation dynamics mediated by riluzole. The reported effects of experimental application of tetrodotoxin and riluzole in respiratory circuits are diverse and seemingly contradictory and have led to considerable debate within the field as to the specific role of  $I_{NaP}$  in respiratory circuits. The results of our simulations provide a mechanistic explanation for seemingly contradictory experimental results from in vitro studies of  $I_{NaP}$  block, demonstrate why riluzole application may fail to effectively block  $I_{NaP}$  in the intact respiratory network and derive the prediction that effective block of  $I_{NaP}$  by low concentration tetrodotoxin will stop respiratory rhythm generation in the intact respiratory network. These simulations support a critical role for  $I_{NaP}$  in respiratory rhythmogenesis in vivo and illustrate the importance of considering the mechanism of action when interpreting and simulating data relating to pharmacological blockade.

# Water transport through tall trees: A vertically explicit, analytical model of xylem hydraulic conductance in stems

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Trees grow by vertically extending their stems, so accurate stem hydraulic models are fundamental to understanding the hydraulic challenges faced by tall trees. A survey of the literature shows that many tree species exhibit continuous vertical variation in hydraulic traits, variation that is ignored by the standard matric flux potential model generally used for stem hydraulics. To examine the effects of this variation on hydraulic function, we developed a spatially explicit, analytical water transport model for stems that allows many traits to vary continuously along the hydraulic path. The analysis shows that cavitation is a whole-stem emergent property resulting from non-linear pressure-conductivity feedbacks that, with gravity, cause impaired water transport to accumulate along the path. We also see that trees can partly compensate for this effect by growing proportionally more sapwood and building tapered xylem with height, as well as reducing xylem vulnerability only at branch tips while maintaining transport capacity at the stem base.

## Modeling, Estimating, and Quantifying Uncertainty in Heterogenous Cancer Models

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Cancer is known to be a heterogeneous system. Intra-tumoral heterogeneity can be modeled by assuming that some parameters in an underlying dynamical system are not constants, but are probabilistically distributed across the population. For example, in a reaction-diffusion equation we can model phenotypic heterogeneity by assuming that the parameters describing diffusion and proliferation are random variables with an underlying distribution. We present techniques for the inverse problem, and estimation, of those probability distributions using aggregate spatio-temporal data for the model system of Glioblastoma Multiforme (GBM). In addition, we quantify the uncertainties in the resulting estimated probability distributions and discuss the amount of data needed to obtain tight estimates.

## Building an academic learning community between biology and statistics

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To enhance the Biology undergraduate education, we create a learning community between Ecology and (introductory) Biostatistics courses. Biology students need more analytical and statistical skills to analyze biological data and more opportunities to apply their knowledge to real-life situations. Thus, this newly implemented High Impact Practice aims to challenge students to achieve beyond their current ability levels and to provide them opportunities to discover the relevance of learning through life applications. In this talk, the overview of the learning community will be briefly introduced. In particular, a couple of biostatistics lectures, in which ecology course contents and case-studies (at least 25% of the course) are directly implemented, will be presented. Then the learning outcomes corresponding to selected activities and methods to assess these outcomes will be discussed. Our pre- and post-assessment data clearly demonstrate that group in this learning community has improved their knowledge much more than regular groups without it despite that the former group had weaker foundations at the beginning. Also, more than half of students on the post-survey agreed that the learning community allowed them to have opportunities to reflect and integrate learning among the two courses, acknowledging the benefits of the learning community. At the end of talk, some possible directions or changes for improvements will be discussed.

## Underlying strain space structure and influenza A eco-evolutionary dynamics

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Influenza A viruses (IAVs) yearly infect a substantial fraction of the human population. These viruses are continually evading host immune pressures, aided through mutations in the immunodominant hemagglutinin (HA) surface protein. Thus, IAV evolution occurs on similar time scales as transmission dynamics, and therefore evolutionary processes must be included in transmission models. Furthermore, IAV evolution is constrained by certain biophysical properties of the HA protein. How does the underlying strain space imposed by this fundamental constraint shape eco-evolutionary dynamics? In this talk, we formulate a mathematical model for IAV evolution and transmission dynamics that spans across scales, from molecular properties of the HA to within-host and global processes. In particular, we focus on HA protein stability, mutation, cross-immunity, and population transmission. By keeping track of infectious individuals with each strain, our formulation imposes inherent population structure through its strain space. With different underlying strain spaces, we investigate the resulting long-term dynamics. To contrast with no structure, we also compare our results to the best fit neutral model of biodiversity. Furthermore, certain sites in the HA are hidden from host immune systems, but still impact protein stability. We investigate network dynamics that occur from “hiding” certain HA sites from immune systems, in addition to population dynamics resulting from this self-organization.

## Assessing Weather Effects on *Aedes aegypti* Population in Brazil

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Vector-borne diseases are an important concern in tropical countries due to the favorable conditions of development and proliferation of these vectors. Particularly, the *Aedes aegypti* mosquito is responsible for the transmission of several diseases. Due to its urban characteristics and competence in spreading diseases, the increase of mosquito population has become a public health problem. Several studies point to the relationship between environmental variables such as temperature, precipitation, and humidity for mosquito development. In this work, we propose a model of ordinary differential equations to investigate the influence of temperature and precipitation on the abundance of mosquitoes. The modeling comprises the aquatic phase - eggs, larvae and pupae - and the adult phase of mosquitoes. Databases of eggs and adult mosquitoes collected for five cities in Brazil were used to verify the applicability of the model in different scenarios. Correlation tests were carried out to verify the robustness of the mathematical model in capturing mosquito abundance patterns for each city. The results showed that the mathematical model was able to capture the behavior observed by the traps in the majority of cases, showing the robustness in different environmental conditions considered for each city.

## A Mathematical Model for Muscle Wasting in Cancer Cachexia

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Cancer cachexia is a severe condition characterized by the irreversible loss of skeletal muscle and adipose tissues, that is estimated to affect more than 50-80% of advanced cancer patients, and to be responsible for 30% of all cancer related mortalities [<http://www.cancercachexia.com/epidemiology-hcp>]. The standard understanding of cachexia is based on nutritional arguments, and thus describes a deregulated cellular metabolism. As such, existing mathematical models focus on metabolic balances. However, a new appreciation is forming for cancer-derived signaling factors that circulate through the host and may disrupt tissue function and homeostasis. Here, we present a novel mathematical model to explore the role of systemic cancer signaling in the development of cachexia. The model describes stem-cell regulated muscle tissue using ordinary differential equations and feedback control. I will discuss our model parameterization strategy, and then present model predictions on potential effects of cancer-derived factors through numerical simulation and sensitivity analysis. We then use our combined modelling results to identify potential treatment options. As no known cure exists for cancer cachexia, it is hoped that uncovering cancer-derived systemic factors that deregulate tissue homeostasis, will lead to the development of new targeted therapies with the potential to impact quality of life for cancer patients.

## Comparing the Eulerian and Lagrangian Spatial Models for Vector-Borne Disease Dynamics

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When it comes to pathogen transmission, movement is an important factor to consider as it determines who becomes exposed to a pathogen. Studies have demonstrated how a vector-borne disease may persist in locations where the abundance of the vector is low, which can be attributed to the host coming from an area of high transmission. In addition, the movement of the vectors contributes to the spread of the disease locally. Considering the movement of both host and vectors in a model, the scale in which they move are significantly different as a vector can only travel short distances. In this talk, we examine the relationship between the Eulerian and Lagrangian approaches for modeling movement of vector-borne diseases in discrete space. We will look at two scenarios: a model in which the host and vector move according to the Eulerian framework, and another model where host moves with respect to the Lagrangian framework and the vector moves with respect to the Eulerian framework.

# A FLEXIBLE NUMERICAL METHOD FOR THE BIFURCATION ANALYSIS OF STRUCTURED POPULATION MODELS

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Structured population models can often be formulated as delay equations, in particular as renewal equations or delay differential equations. In order to understand the dynamical properties of the systems and especially the influence of parameter variation on the dynamical behavior (i.e., the bifurcation properties), it is fundamental to have numerical tools at disposal. Pseudospectral discretization has proved to be an effective and flexible technique for the numerical bifurcation analysis of delay equations. I will briefly present the main ideas underlying the numerical method and then illustrate its potential and flexibility by means of some example models from population dynamics and epidemiology. This is based on a series of studies in collaboration with Dimitri Breda (Udine), Odo Diekmann (Utrecht), Mats Gyllenberg (Helsinki), Rossana Vermiglio (Udine).

## Using phase space to map the trajectory of infections

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We are interested in limiting the impact of infectious diseases. We want to limit the extent that people get sick, allow them to survive extreme illness, and ensure that they can recover from infections. To do this, we describe infected hosts as a resilient system and try to quantitate its stiffness (how far health will bend upon infection), its strength (how far health will move before it breaks) and its ability to return to baseline health. We then try to find ways of manipulating the system to fix the variable that is leading to illness. We use a simple mathematical model to describe these properties when we study populations of infected animals. We can use this model to follow infections in the lab where we can measure the disease over time, but we run into trouble when we try to apply this to actual patients. Time is an essential variable in our lab experiments, but we have no access to time information with patients. When a patient shows up at your door, they need to be treated immediately; we can't watch their progress before we intervene and we don't know when the infection started. To overcome this problem, we've been making maps of the trajectories infected hosts take as they pass through their symptoms and move from health, through sickness and back to health. The paths the infected take follow reproducible routes that vary in predictable ways. These routes are mostly unidirectional, but sometimes can appear to run backwards. These paths can be used as clocks to tell both infection time, and where a host is on the infection trajectory. This inspired us to try to build physical clocks that tells infection time. We want to use this clock to show the relationship between symptoms and time and shows what is missing from our model (adaptation) and how we will fix that.

# Controlling disease evolution: models and experiments to understand timescales, trajectories and outcomes.

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Bacterial antibiotic resistance, and chemotherapy resistance in cancer are two of the biggest problems in healthcare in the developed world. The standard approach to these problems is to probe the individual biological mechanisms responsible for the resistance we see. The problem with this, is it puts us in a continuing arms race against these diseases one which they will always win: we can not develop drugs at the same pace at which evolution allows them to innovate. To address this, I claim we should work toward controlling the evolutionary process itself which provides them the opportunity to innovate. To this end, I will present three mathematical models focused on different aspects of the evolutionary process, each with an experimental assay designed specifically for it. First, we will discuss evolutionary game theory and our new game assay designed to measure games between pairs of cell types, *in vitro*. We will then discuss a low-dimensional Fokker-Planck approximation of evolution of resistance with which we have managed to optimize the speed of evolutionary convergence, and a simple assay to validate this, along with higher dimensional simulations. Finally, if we have time, we will show experimental evidence of evolutionary branching under therapy, and discuss how a fitness landscape metaphor can be used to better understand, and even perturb these fate choices.

## Mathematical modeling the process of tumorigenesis

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Carcinogenesis is a complex stochastic evolutionary process. One of the key components of this process is evolving tumors, which interact with and manipulate their surrounding microenvironment in a dynamic spatio-temporal manner. Recently, several computational models have been developed to investigate such a complex phenomenon and to find potential therapeutic targets. In this talk, we present novel computational models to gain some insight about the evolutionary dynamics of cancer. Furthermore, we propose an innovative framework to systematically employ a combination of mathematical methods and bioinformatics techniques to arrive at unique personalized targeted therapies for cancer patients.

## Spreading speeds in random environments

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Integrodifference equations have been widely used to model the invasion of species, the spread of diseases, etc. Traditional models assume that the environment is temporally constant. In this work, we study a class of integrodifference equations with random coefficients in order to understand the consequences of random fluctuations.

## Regulation of nuclear architecture, mechanics and nucleo-cytoplasmic shuttling of epigenetic factors by cell geometric constraints

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Cells sense mechanical signals from their microenvironment and transduce them to the nucleus to regulate gene expression programs. To elucidate the physical mechanisms involved in this regulation, we developed an active three-dimensional chemo-mechanical model to describe the three-way feedback between the adhesions, the cytoskeleton, and the nucleus. The model shows local tensile stresses generated at the interface of the cell and the extracellular matrix (ECM) regulate the properties of the nucleus, including nuclear morphology, levels of lamin A,C and histone deacetylation, as these tensile stresses (i) are transmitted to the nucleus through cytoskeletal physical links, and (ii) trigger an actomyosin-dependent shuttling of epigenetic factors. We then show how cell geometric constraints affect the local tensile stresses and subsequently the three-way feedback and induce cytoskeleton-mediated alterations in the properties of the nucleus such as nuclear lamina softening, chromatin stiffening, nuclear lamina invaginations, increase in nuclear height and shrinkage of nuclear volume. We predict a phase diagram that describes how the disruption of cytoskeletal components impacts the feedback and subsequently induce contractility-dependent alterations in the properties of the nucleus. Our simulations show that these changes in contractility levels can be also used as predictors of nucleo-cytoplasmic shuttling of transcription factors and the level of chromatin condensation. The predictions are experimentally validated by studying the properties of nuclei of fibroblasts on micropatterned substrates with different shapes and areas.

## Comparing temperature-dependent transmission models for 16 mosquito-borne diseases

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Temperature is a key driver of mosquito-borne disease because it affects the physiology and life history traits of mosquitoes and the pathogens they transmit. These trait thermal responses are typically non-linear, unimodal, and vary by mosquito and pathogen species. We parameterized trait-based models for transmission of 16 vectorpathogen systems for which published temperature-dependent trait data exist. For all systems, transmission responded unimodally to temperature. Transmission at high temperatures was almost always constrained by short adult mosquito lifespans, while transmission at low temperatures was constrained by a variety of traits, including pathogen development rate, vector competence, and mosquito demographic traits. The specific temperatures of the optima and limits for transmission varied across vector and pathogen species. Much of this variation was idiosyncratic, but there were also systematic differences between systems with primarily temperate and tropical distributions. As expected based on geography, most temperate systems exhibit cooler optima and lower thermal limits, and wider thermal breadths, than the tropical systems. These temperature-dependent transmission models (from lab-based trait data) successfully predict seasonal and geographic patterns of disease observed in independent human case data. In particular, county-level incidence of WNV in the US shows a clear unimodal response to average summer temperatures, peaking near the intermediate optimum predicted by the trait-based model (24°C and 25°C, respectively). Together, the predictive transmission models and observed patterns of disease provide strong evidence for the role of temperature in driving transmission of mosquito-borne diseases. Quantitative, trait-based models for temperature-dependent transmission are critical for predicting future patterns of disease due to climate change, particularly since future temperature regimes may exceed currently observed conditions. In general, we expect shifts in mosquito-borne disease: warming will increase transmission in settings below thermal optima but decrease transmission in settings above thermal optima.

# Impact of Asymmetric Movement on Population Dynamics

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Spatial heterogeneity and spatial movement play an important role in population dynamics. Such movement in a heterogeneous environment or network could be symmetric or asymmetric (biased), and the resulting mathematical model can be regarded as a dynamical system on network. The impacts of asymmetric movement (versus symmetric movement) on population dynamics will be investigated using several ecological and epidemiological models from the literature. The analytical results rely on a successful employment of tools from differential equations, dynamical systems to matrix theory and graph theory, while numerical simulations highlight the need of a better understanding of dynamical systems on networks.

Embedded ODE Model for the 2014 Ebola Outbreak in West Africa; An analysis of Guinea,  
Liberia & Sierra Leone

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During the 2014 Ebola outbreak in West Africa, extreme poverty, a dysfunctional health care system, a distrust in government by citizens, delayed responses and local burial customs contributed to the epic proportions of individuals effected by the disease. With a high case fatality rate and 57 - 59% of deaths from reported cases occurring in hospitals, it is imperative that the medical community have a more informed understanding of the most influential methods by which the disease spread. We utilize a branching SEIR Ebola model to determine the prominent forces of infection causing the outbreak. The deterministic model is embedded into a stochastic process by means of a novel multinomial distribution derivation and fitted to publicly available data, provided by the World Health Organization, allowing uncertainty to be quantified within parameter estimations. Results indicate rates of transmission from the infectious community and the hospitalized & infectious community to be low within the most effected countries, Guinea, Liberia and Sierra Leone. The rate of transmission from the deceased & infectious population is high in Guinea. The frequency for which infectious individuals enter the hospital is significantly low in Guinea and Sierra Leone. The large discrepancies between these parameter values among the countries indicates a need for mitigation strategies to be focused on earlier hospitalization and proper burial procedures which respect cultural beliefs.

## Should Wildflowers be Planted In or Around Blueberry Farms?

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Bumble bees are better pollinators for blueberry flowers than honey bees. However, bumble bees have been observed to prefer nectar and pollen from wildflowers than blueberry flowers in regions where they are found. Blueberry growers in the Okanagan region in Canada are progressively introducing bumble bees in their farms to replace the traditional use of honey bees as pollinators; but these growers are often concerned with the proportion of wildflowers to plant relative to blueberry crops. Growers are also concerned with the locations for ‘planting’ wildflowers for an optimal pollination service of blueberries. We develop a mathematical model that accounts for the various stages of bumble bees life and foraging cycles in order to propose solutions to the growers concerns.

## Mathematical Modeling and Statistical Inference to Quantify Product Inhibition in Chromogenic Assays

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Chromogenic substrates (CS) are synthetic substrates used to monitor the activity of a target enzyme. It has been reported that some CSs display competitive product inhibition with their target enzyme. Thus, in assays where enzyme activity is continuously monitored over long periods of time, the product inhibition may significantly interfere with the reactions being monitored. Despite this knowledge, it is rare for CSs to be directly incorporated into mathematical models that simulate these assays. This devalues the predictive power of the models. In this study, we examined the interactions between a single enzyme, coagulation factor Xa, and its chromogenic substrate. We developed, and experimentally validated, a mathematical model of a chromogenic assay for factor Xa that explicitly included product inhibition from the CS. We employed Bayesian inference, in the form of Markov-Chain Monte Carlo, to estimate the strength of the product inhibition and other sources of uncertainty such as pipetting error and kinetic rate constants. Our model, together with carefully calibrated biochemistry experiments, allowed for full characterization of the strength and impact of product inhibition in the assay. The effect of CS product inhibition in more complex reaction mixtures was further explored using mathematical models.

## Balances and features underlying intrinsic theta generation in the hippocampus

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Oscillatory activities are a ubiquitous feature of brain recordings and likely form part of the neural code. In particular, theta rhythms (3-12Hz) in the hippocampus play fundamental roles in memory processing. Can we understand how theta rhythms are generated from cellular perspectives? It is challenging to address this question largely because of the multi-scale nature of our brains. However, we need to tackle this challenge as it is clear that cellular specifics can dictate oscillatory network output and thus contribute to brain function and neurological disease.

By focusing on a whole hippocampus preparation that spontaneously expresses theta rhythms, we constrained excitatory and inhibitory cellular models, network size and connectivity based on the experimental data, and were able to obtain a mechanistic understanding of how these rhythms could arise. In exploring the robustness of the mechanism with excitatory-inhibitory balances derived from experiment, we find that post-inhibitory rebound and rheobase features in the excitatory cells are key aspects to the generation of these rhythms in excitatory-inhibitory networks. As links with detailed, biophysical models are possible, these considerations help lead to explanations and understanding of theta rhythm generation in the hippocampal system.

## Predicting Viral Loads, Host Response, Pathology, and Disease Severity During Influenza

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Influenza A viruses cause a significant amount of morbidity and mortality. Understanding how the infection is controlled by host immune responses and how different factors influence severity are critical to combat the infection. During infection, virus increases exponentially, peaks, then declines until resolution. The viral decline is often biphasic, which we previously determined is a consequence of density-dependent infected cell clearance. The second, rapid clearance phase corresponds with the infiltration of CD8 T cells, but how the rate changes with infected cell density and CD8 density is unclear. Further, neither of these kinetics directly correlate to disease severity. Thus, we investigated these relations by infecting mice with influenza A/PR8, simultaneously measuring virus and CD8s, and developing/calibrating a kinetic model. The model predicts that virus resolution is sensitive to T cell expansion, that there is a critical CD8 magnitude below which the infection is significantly prolonged, and that the efficiency of CD8-mediated clearance is dependent on infected cell density. To further examine this finding and validate the model, we quantified infected cells kinetics using histomorphometry. These data showed that the area of lung infected reflects the predicted infected cell dynamics, and that the infection resolution dynamics parallel the relative CD8 magnitude. Our analysis further revealed a nonlinear relation between disease severity and the percent damaged lung. Establishing these critical connections that map the kinetics of virus, infected cells, T cells, lung pathology, and disease severity aids our ability to predict the course of infection, disease progression, and potential complications.

## Photosynthetic acclimation through the lens of optimality

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Terrestrial photosynthesis is the largest flux of carbon dioxide between the atmosphere and the Earth's surface. Photosynthesis is a dynamic process that shows strong acclimation to environmental conditions, making predictions difficult under non-stable environments. Optimality theory provides an avenue for predicting photosynthetic acclimation. Here, we present a novel theory of optimal plant photosynthesis for C<sub>3</sub> and C<sub>4</sub> species. We then multiple studies using the theory as a null model to help better understand acclimation processes over space and time. Specifically, we use the theory to show that photosynthetic acclimation to elevated CO<sub>2</sub> is driven almost exclusively by optimal down-regulation of Rubisco carboxylation capacity, without consideration of nutrient availability constraints. This result runs counter to predictions from the progressive nutrient limitation hypothesis. We also find that nutrient availability has little impact on leaf-level photosynthesis, in line with prediction from optimality, but that soil nutrition stimulates whole-plant photosynthesis by increasing leaf area. Finally, we find that C<sub>4</sub> photosynthesis is not likely to be more advantageous than C<sub>3</sub> photosynthesis in the future under most conditions. These results demonstrate the power of optimality theory for elucidating the mechanisms underlying plant physiological process responses to variable environmental conditions.

## Modelling the Effects of Stigma on Leprosy

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The World Health Organizations leprosy-elimination campaign has significantly reduced global leprosy prevalence, but approximately 214,000 new cases of leprosy are reported each year. An ancient and neglected affliction, leprosy is also one of the most heavily stigmatised diseases of all time. We developed a mathematical model to examine the effects of stigma on sustaining disease transmission, using low and high degrees of stigma, as well as in its absence. Our results show that stigma does indeed play a central role in the long-term sustainability of leprosy. We also examined sensitivity of the outcome to all parameters and showed that the effects of stigma could increase the number of infected individuals by a factor of 80. Therefore both targeted education and shifts in cultural attitudes towards leprosy will be necessary for the eventual eradication of the disease.

## Exploiting ecological dynamics to overcome cancer therapy resistance

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Cancer progression is grounded in principles of evolutionary and ecological theory. Just like any other individual in a population, individual cancer cells compete for space and resources. Diverse populations of cancer cells are selected based on the ever-changing ecological landscapes of the tumor microenvironment and physico-chemical parameters of the space in which the cancer cells reside. In the context of treatment, the therapy itself imposes a strong selective force in which only a subset of cancer cells are able to survive. While it is clear that therapy-resistant cells have a fitness advantage in the context of drug treatment, there are also likely to be substantial fitness costs associated with the acquisition of a therapy-resistant phenotype. This 'collateral sensitivity' to alternate drugs supports the notion that evolutionary trade-offs exist in the context of cancer therapy that can be therapeutically exploited. We sought to apply a similar strategy to the problem of enzalutamide resistance in prostate cancer. Enzalutamide is a novel hormonal agent that targets the androgen receptor. These hormonal therapies have significantly prolonged survival of men with metastatic, castration-resistant prostate cancer; however, acquired resistance to these drugs within one to two years is nearly universal. To overcome this substantial clinical challenge, we wished to understand the evolutionary and ecological fitness dynamics of enzalutamide-resistant prostate cancer with the goal of identifying therapeutic vulnerabilities of enzalutamide-resistant disease. To do this, we combined preclinical models of enzalutamide resistance with real-time imaging to track the fitness dynamics of resistant and sensitive cells. Enzalutamide-resistant cells had a significant fitness advantage in the presence of drug and, surprisingly, were equally fit as compared to enzalutamide-sensitive cells when drug was removed. Yet, despite their equal fitness in the absence of drug, the enzalutamide-resistant cells displayed a dramatic fitness disadvantage in the presence of glucose deprivation. This sensitivity to nutrient deprivation was mediated by changes in fatty acid metabolism, stress response signaling, and migration/invasion pathways. Our current work using an ecological and evolutionary framework, highlights a potential vulnerability that can be exploited to treat therapy-resistant prostate cancer.

# Is There a Risk of Chikungunya Outbreak with Autochthonous Transmission in Ontario Canada?

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Chikungunya is a mosquito-borne disease which is transmitted by Aedes mosquitoes. In 2014, Chikungunya spread across Caribbean, Central America and South America with an obvious trend to move north of the globe. Adult Aedes aegypti and Aedes albopictus mosquitoes were captured in Windsor in summer of 2016 and 2017, which suggests that the Aedes of mosquito species may be becoming established in Canada in the future when it is getting warmer.

To assess the risk of Chikungunya outbreak with autochthonous transmission in Canada, we developed a transmission model for Chikungunya virus, transmission model with maturation delay for mosquito reproduction, extrinsic incubation delay and intrinsic incubation delay due to the impact of temperature. The basic reproduction number was computed to evaluate the effect of temperature on the risk of Chikungunya transmission in Canada. Dynamical analysis shows that maturation delay may destabilize the infected steady state through Hopf bifurcation. However, extrinsic incubation delay and intrinsic incubation delay do not affect the stability of the infected steady state, but alter the peaking time and number of infected humans. The temperature-derived risk classes for Chikungunya transmission in Canada were created based on the effect of temperature on maturation period and extrinsic incubation period. Using our model and basic reproduction number, we generated the risk map of Chikungunya with temperature and found that there is an increasing risk of the virus in the areas further north and west of Ontario if global warming continues. These findings suggest that through its effect on mosquito reproduction and Chikungunya virus transmission, climate change will broaden the range of risk in Canada. This is a joint work with Huaiping Zhu, Nicholas Ogden, Erin Rees, Ziwang Deng, Min Weng and Zhen Jin.

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Title:

QSP model development for receptor-mediated immuno-oncology therapies

Abstract:

Several immuno-oncology (IO) therapies, such as PD1/L1 checkpoint inhibitor, target coreceptors on immune cells. Many of these coreceptors are ideal drug candidates as they can modulate the activity or expansion of immune cells to increase tumor killing. However, several factors must be considered to evaluate IO therapies that target coreceptors such as 1) the cell surface coreceptor expression varies across different immune cells, 2) the temporal expression of different coreceptors on immune cells range from transient to long-lasting upon activation with antigen presenting cells, and 3) the coreceptor-modulated expansion of immune cells varies across the numerous coreceptor types. Thus, it is important to model coreceptor dynamics and effects of its modulation in detail to determine drug efficacy, dose, and schedule for mono- or combination-therapy. I will present how we developed the cell-cell and receptor-ligand interaction framework that can be applied to number of different coreceptors and how this framework integrates with a broader IO quantitative systems pharmacology (QSP) platform. I will also provide insights obtained using QSP modeling on coreceptor levels and immune cell activation in different tissues that has an impact on drug dosing and efficacy.

# A computational framework for a Lyapunov-enabled analysis of biochemical reaction networks

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Complex molecular biological systems can be described in principle by reaction networks that explicitly take into account the sophisticated network of chemical interactions regulating cell life. Unfortunately, the effective utilization of such descriptions is often hindered by a pervasive problem: despite the wealth of qualitative graphical knowledge about network interactions, the form of the governing nonlinearities and/or the values of kinetic constants are hard to uncover experimentally. They can also change with environmental variations. Thus, it is desirable to have a theoretical framework to robustly guarantee the behavior of such networks, based only on graphical knowledge and applying regardless of the particular form of kinetics. This paper introduces a class of networks that are “structurally (mono) attractive” by which we mean that they are incapable of exhibiting multiple steady states, oscillation, or chaos by virtue of their reaction graphs. These networks are characterized by the existence of a universal energy-like function which we call a Robust Lyapunov function (RLF). To find such functions, a finite set of rank-one linear systems is introduced, which form the extremals of a linear convex cone. The problem is then reduced to that of finding a common Lyapunov function for this set of extremals. Based on this characterization, a computational package, Lyapunov-Enabled Analysis of Reaction Networks (LEARN), is provided that constructs such functions or rules out their existence. An extensive study of biochemical networks demonstrates that LEARN offers a new unified framework. We study basic motifs, three-body binding, and transcriptional networks. We focus on cellular signalling networks including various post-translational modification cascades, phosphotransfer and phosphorelay networks, T-cell kinetic proofreading, ERK signaling, and the Ribosome Flow Model. networks.

## Mechanistic Modeling for Hypothesis Testing in Preclinical Immuno-Oncology Drug Discovery

Authors: Derek Bartlett and Mary E. Spilker\*

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**Abstract:** The ability to harness an individual's immune system against cancer holds significant promise for patients. However, from a drug discovery and development perspective, it presents substantial challenges as the industry strives to understand the complex mechanisms and biological variability existing within preclinical test systems and humans. This presents an opportunity for modeling and simulation methods to capture the current knowledge of the relevant biology and explore its complex dynamics with and without therapeutic interventions using in silico approaches. These in silico predictions can then be tested against experimental data to confirm or refine our understanding. To demonstrate the use of modeling and simulation methods for hypothesis testing in preclinical drug discovery, mathematical approaches focused on therapeutic modulation of the immune response, including antigen presentation and T cell function, for immuno-oncology applications will be presented.

## Comparing Intervention Strategies for Reducing *Clostridium difficile* Transmission: An Agent-Based Modeling Study

Brittany Stephenson<sup>\*a</sup>, Cristina Lanzas<sup>b</sup>, Suzanne Lenhart<sup>c</sup>, Eduardo Ponce<sup>d</sup>, Jason Bintz<sup>e</sup>, and Judy Day<sup>f</sup>

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In recent years, healthcare facilities have experienced an increasing substantial burden from the toxin-producing bacteria *Clostridium difficile*, which can cause severe intestinal disease. This bacteria can survive for extended periods of time on hospital surfaces. In this talk, I will discuss the development of an agent-based model that simulates the transmission of *C. difficile* in a healthcare setting and considers contributions of the pathogen from environmental surfaces. This model explicitly incorporates healthcare workers (HCWs) as vectors of transmission, tracks individual patient antibiotic histories, incorporates varying risk levels of antibiotics with respect to CDI, and tracks contamination levels of ward rooms by *C. difficile*. I will also discuss how we used the model to evaluate the efficacy of a variety of control interventions and combinations of interventions on reducing *C. difficile* nosocomial colonizations and infections. The control techniques include two forms of antimicrobial stewardship, increased environmental decontamination through room cleaning, improved HCW compliance, and a preliminary assessment of vaccination.

# Stem cell niche dynamics in human blood cancer - insights from mathematical modeling

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Acute myeloid leukemia (AML) is one of the most aggressive blood cancers. The cancer originates from a small population of so called leukemia stem cells (LSC) that survive treatment and trigger relapse. So far it is an open question how LSC interact with the hematopoietic stem cells (HSC) that are responsible for blood cell production. This interaction is of crucial importance to understand disease dynamics and treatment failure. It is known that HSC reside in a protective bone marrow niche that is required to maintain HSC function. There is evidence from model organisms that LSC out-compete HSC from the niche. Due to experimental limitations it is challenging to determine whether a similar mechanism exists in humans. We develop mathematical models that describe interactions of HSC and LSC. These models allow to study how processes in the stem cell niche impact on observable clinical parameters. Using a combination of computer simulations and patient data we provide evidence that human HSC and LSC compete for spaces in a joined bone marrow niche and that LSC can dislodge HSC. We further use the model to obtain insights into inter-patient heterogeneity and to assign patients to different risk groups.

We consider the following questions:

- How can we use mathematical models to study competition of LSC and HSC in the human bone marrow niche?
- How can we quantify LSC-HSC competition? What is its impact on disease dynamics? How does it differ between patients?
- What can model-based evaluation of clinical data tell us about the prognosis of individual patients?

## Modeling movement and persistence of small organisms in flow

Christopher Strickland (speaker)<sup>a</sup>, Laura Miller<sup>b</sup>, Kemal Ozalp<sup>c</sup>, Thomas Dombrowski<sup>d</sup>

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Small organisms often have outsized impact on the ecosystem they inhabit and represent both a complex and interesting system to model mathematically. Heterogeneous flow fields and biological protective layers are two major factors influencing organismal behavior with macroscale implications. In this talk, I will describe a data-driven approach to better understanding this system, including the use of a newly developed agent-based modeling framework, Planktos, which provides an object-oriented code base for examining the effects of organismal behavior in flow.

# Impact of Disparity in Vaccination Coverage on Disease Transmission in the Setting of Multiple Patches

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The research background is introduced; a simple metapopulation model with explicit movement of individuals between patches is formulated, in which there exist two levels of vaccination coverage; a threshold, separating disease establishment from its extinction, is obtained through analytical analysis; the important role of disparity in vaccination coverage is highlighted in determining the dynamics of epidemiology; brief numerical considerations follow in the end.

## Using MRI to Predict Drug Distribution in Glioblastoma Patients

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Clinical neuro-oncology relies on the hyperintensity of gadolinium (Gd) contrast agent on magnetic resonance imaging (MRI) in tumor regions to confirm that the blood-brain barrier (BBB) is locally compromised. While the extent of Gd hyperintensity may indicate that systemically-administered drug is being distributed to the tumor regions, little is known about how a drug is distributed and how it may relate to the Gd hyperintensity. Additionally, glioblastomas (GBMs) are diffusely invading neoplasms with a significant fraction of the overall tumor cells spread peripheral to the Gd abnormality, which raises uncertainty as to how or if the rest of the diffuse tumor is affected by drug. Given the gap in understanding drug delivery to the brain, we propose a quantitative approach to mathematical model drug delivery in GBM based on MRI and matrix-assisted laser desorption/ionization mass spectroscopy imaging (MALDI). By developing a quantitative understanding of drug distribution, we can make more robust predictions regarding treatment efficacy in the clinical setting.

## Inverse problem for dynamical systems arising from mathematical immunology

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In mathematical immunology, data used for fitting and validation of dynamical system models are frequently aggregated from multiple experimental subjects. The problem of estimation of parameters from discrete data then reduces to the problem of mapping data density to the parameter space. I will present recent developments in this area, including analytical and numerical estimates of the maximal permissible uncertainty in the data for which the qualitative features of the inverse problem solutions persist, and the importance of Jacobian in the estimation of uncertain parameters from data distributions. I will show examples of parametrized models of in-host response to influenza infection and bacterial pneumonia.

## Modelling Antibody-Dependent Enhancement (ADE) between DENV and ZIKV

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As ZIKV and DENV belong to the same Flavivirus family, structural similarities between them leads to the induction of cross-reactive responses, like antibody-dependent enhancement (ADE). There is experimental study showing that ZIKV exposed macaques present the high level of DENV cross-reactive binding antibody with a low DENV neutralizing activity, indicating the occurrence of the enhancement of dengue infection. Similarly, the DENV-specific antibodies can also bind ZIKV but were unable to neutralize the virus. Considering the ADE effect in different scales, this talk includes two parts. Firstly, I will talk about, in the population level, how dengue vaccination may affect ZIKV infection dynamics and how the sexual transmission of ZIKV affect the dynamics of both DENV and ZIKV with antibody-dependent enhancement. Secondly, I tried to model the impact of ADE on the virus dynamics.

This talk is based on the joint works with Xi Huo, Yanni Xiao, Shigui Ruan, and Jianhong Wu.

# Capturing the Gonotrophic Cycle Contributions in a Mosquito Demographic focused Mathematical Model for Malaria

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A modelling framework that describes the dynamics of female *Anopheles sp* mosquito population is developed and analyzed. The framework includes a characterization of the gonotrophic cycles of the female mosquito population. An understanding of how the gonotrophic cycles impact the quantification of basic thresholds such as the basic offspring number and the disease reproduction number is explored and investigated. Initial analysis of the model illustrate that newly emerged mosquitoes that are infected with the malaria parasite during their first blood meal play an important and strong role in the malaria disease dynamics. Additionally, mosquitoes at later gonotrophic cycle stages also impact the dynamics but their contributions to the total mosquito population size decreases with increasing number of gonotrophic cycles. The size of the contribution into the young mosquito population is also dependent on the length of the gonotrophic cycles, an important bionomic parameter, as well as on how the mosquitoes at the final gonotrophic cycles are incorporated into the modelling scheme. Questions relating to emergent phenomena and biological principles will be discussed.

**Learning from memory: a computational model for a logarithmically compressed timeline of the past and future**

Zoran Tiganj

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Recent theoretical work has focused on developing a unifying computational model of memory, timing and prediction. Following up on this work, I will present a computational mechanism for computing a scale-invariant timeline of future outcomes. This mechanism efficiently computes an estimate of inputs as a function of future time on a logarithmically-compressed scale, and can be used to generate a scale-invariant power-law-discounted estimate of expected future reward. The representation of future time retains information about what will happen when and it is computed from a logarithmically-compressed timeline of the past (memory representation) that retains information about what happened when.

## Combined model of network spread and protein aggregation recapitulates the spatiotemporal progression in Alzheimer's disease

Ashish Raj<sup>a</sup>, Xiao Gao<sup>b</sup>, Justin Torok<sup>c</sup>, Veronica Tora<sup>d</sup>, Bruno Franchi<sup>e</sup> and J Lyoo<sup>f</sup>

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Alzheimer's disease involves widespread and progressive deposition of misfolded protein tau, first appearing in the entorhinal cortex, coagulating in longer polymers and insoluble fibrils. There is mounting evidence for "prion-like" trans-neuronal transmission, whereby proteins misfold, trigger misfolding of adjacent same-species proteins, and there-upon cascade along neuronal pathways, giving rise to networked spread along white matter projections. But the cause-effect mechanisms by which various oligomeric  $\tau$  species are produced, aggregate and disseminate are unknown. The question of how protein aggregation and subsequent spread lead to stereotyped progression in the Alzheimer brain remains unresolved.

We present here mathematically precise parsimonious modeling of these pathophysiological processes, extrapolated to the whole brain. We model all three key processes:  $\tau$  monomer production; aggregation into oligomers and then into tangles; and the spatiotemporal progression of misfolded  $\tau$  as it ramifies into neural circuits via the brain connectome. We model monomer seeding and production at the entorhinal cortex, aggregation using Smoluchowski equations; and networked spread using our prior Network-Diffusion model, whereby anatomic connections govern the rate at which two distant but connected brain regions can transfer pathologic  $\tau$ . This combined model, which we call Aggregation-Network-Diffusion (AND), exhibits all hallmarks of tau progression seen in human patients. Unlike previous theoretical studies of protein aggregation, we provide validation on experimental *in vivo* imaging and fluid tau measurements from large datasets. The model accurately captures not just the spatial distribution of empirical regional tau and atrophy, but also patients' cerebrospinal fluid phosphorylated tau profiles as a function of disease progression. This unified quantitative and testable model may have the potential to explain observed phenomena and serve as a test-bed for future hypothesis generation and testing *in silico*.

# A Mechanism for Epithelial-Mesenchymal Heterogeneity in Cancer Cell Populations

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Epithelial-mesenchymal heterogeneity implies that cells within the same tumor can exhibit different phenotypes—epithelial, mesenchymal, or one or more hybrid epithelial-mesenchymal phenotypes. This behavior has been reported across cancer types, both *in vitro* and *in vivo*, and implicated in multiple processes associated with metastatic aggressiveness including immune evasion, collective dissemination of tumor cells, and emergence of cancer cell subpopulations with stem cell-like properties. However, the ability of a population of cancer cells to generate, maintain, and propagate this heterogeneity has remained a mystifying feature. Here, we used a computational modeling approach to show that epithelial-mesenchymal heterogeneity can emerge from the noise in the partitioning of RNAs and proteins among daughter cells during the division of a cancer cell. Our model captures the experimentally observed temporal changes in the fractions of different phenotypes in a population of murine prostate cancer cells, and describes the hysteresis in the dynamics of epithelial-mesenchymal plasticity. The model is further able to predict how factors known to promote a hybrid epithelial-mesenchymal phenotype alter the phenotypic composition of a population. Finally, we used the model to probe the implications of phenotypic heterogeneity for different therapeutic regimens and found that co-targeting of epithelial and mesenchymal cells is likely to be the most effective strategy for restricting tumor growth. By relating the dynamics of an intracellular circuit to the phenotypic composition of a population of cancer cells, our study serves as a first step towards understanding the generation and maintenance of non-genetic heterogeneity in a population of cancer cells, and towards the therapeutic targeting of phenotypic heterogeneity and plasticity in cancer cell populations.

# Convergence to equilibrium for a complex balanced system with boundary equilibria

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We shall discuss the rate of convergence to the complex balanced equilibrium for a three-species chemical reaction-diffusion system with boundary equilibria in some stoichiometric classes, and whose right hand side is bounded above by a quadratic nonlinearity in the positive orthant.

# Combining Population Modeling and Bayesian Inference for Tumor Growth Prediction

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Tumor growth curves are classically modeled by ordinary differential equations. In analyzing the Gompertz model several studies have reported a striking correlation between the two parameters of the model. Although this observation is still under debate, it might imply a constant maximal tumor size within a given species.

We analyzed tumor growth kinetics within the statistical framework of nonlinear mixed-effects (population approach). This allowed for the simultaneous modeling of tumor dynamics and inter-animal variability. Experimental data comprised three animal models of breast and lung cancers, with 843 measurements in 94 animals. Candidate models of tumor growth included the Exponential, Logistic and Gompertz. The Exponential and Logistic models failed to describe the experimental data whereas the Gompertz model generated very good fits. The population-level correlation between the Gompertz parameters was further confirmed in our analysis ( $R^2 > 0.96$  in all groups), suggesting a reduction of the number of degrees of freedom of the Gompertz model. Combining this structural correlation with rigorous population parameter estimation, we propose a novel reduced Gompertz function consisting of a single individual parameter. We assessed the descriptive power of the reduced Gompertz model and found that performances were similar to the two-parameters Gompertz equation. We then considered the problem of predicting the initiation time of a tumor from only three late measurements, comparing the results arising from Bayesian inference and from likelihood maximization. Thanks to its simplicity, the reduced Gompertz model showed superior predictive power. In addition, drastic improvements were observed when leveraging population priors using Bayesian inference as compared to likelihood maximization alone, for both accuracy and precision. Specifically, mean accuracy was 12.7% versus 88.5% and mean precision was 15.6 days versus 242 days, for the breast cancer cell line.

These results offer promising clinical perspectives for the personalized prediction of tumor age from limited data at diagnosis. In turn, such predictions could be helpful for assessing the extent of invisible metastasis at the time of diagnosis.

## The effect of small and unvaccinated subpopulations on polio elimination

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Polio eradication efforts have reduced the regions of endemic circulation down to Pakistan, Afghanistan, and Nigeria. One of the challenges involved in eliminating polio in these regions is that political conflict has the potential to form isolated subpopulations, making vaccination and reporting of symptomatic cases (surveillance) challenging. Additionally, polio can circulate without detection in a population because few infections are symptomatic and those that have already had a poliovirus infection are asymptomatic during subsequent infections. Asymptomatic transmission coupled with poor surveillance can make it difficult to determine when the virus has gone extinct in a population. We use a discrete-individual stochastic counting process model of polio to access the impact that small and unvaccinated subpopulations may have as countries move towards elimination. We consider their effect in the context of a well-mixed population as well as within a metapopulation framework.

## Informing Drug Development Questions through Modeling and Simulation: Case Studies in HIV

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Throughout all stages of drug development, questions arise that require integrating data across multiple heterogeneous sources to drive a decision. Informed drug development in HIV requires the application of a full range of models. In early discovery for HIV Cure, quantitative systems pharmacology tools, such as viral dynamics modeling, provide insight into the prospect of new targets and help to develop early clinical trial plans to test different mechanisms. As new HIV treatment drugs move into preclinical development, model-based meta-analyses predict accurate exposure targets which allow for initial dose predictions and rapid phase 1 development. After achieving the exposure target and sufficient safety experience in healthy volunteers, viral dynamics modeling is used to predict the viral load drop for short term monotherapy treatment. Subsequent dosing panels are informed through estimation and simulation cycles with the viral dynamics model that allows for an adaptive clinical design to inform exposure-response. Continuing into late development, physiological based pharmacokinetic modeling (PBPK) and population pharmacokinetic modeling (POPPK) inform on intrinsic/extrinsic factors, including drug interactions and covariates that will affect the exposure of the drug, and clinical trial design, dose selection, and labeling. Finally, in the post approval space, PBPK and POPPK are used to scale efficacious concentrations to special populations, such as pediatrics. These case studies, presented throughout HIV drug development, highlight the uses and impact of modeling and simulation analyses to advance new drugs through development and to impact patient lives.

## The role of animal grazing in the spread of Chagas disease

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Chagas disease is an important neglected tropical disease which causes on average about 70 0 0 deaths per year, and an estimated 25 million people risk of acquiring it. This illness is often found in rural areas, which are usually characterized by poverty and presence of animals which act as reservoirs of the disease. Our main objective is to study the effect of animal grazing on the disease levels of the human population. For this purpose, we consider two environments (domestic and wild) where each one has permanent residents, and there is a proportion of animals that move between both environments due to grazing. This movement is modeled through the residence time in each environment. We analyze the proposed model and finally, we discuss the influence of domestic animals residence time on the disease level of human population.

## Evolutionary responses to a disturbance in a predator-prey system

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In this talk, we study the effect of a prolonged disturbance, such as a toxicant, on predator-prey dynamics. We first derive and analyze a discrete time predator-prey model. We establish conditions for the existence and stability of equilibria, as well as for the persistence of both predator and prey populations. We then extend this model to an evolutionary model to consider the case where the prey species has the potential to evolve in response to a toxicant. To this end, we use evolutionary game theory methodology to couple the dynamics of the populations with the dynamics of a single evolving phenotypic trait that describes the amount of toxicant resistance developed by the prey. The predator is impacted by prey evolution both indirectly and directly, through changes in prey density and through an assumed trade-off between toxicant resistance and the ability of the prey to escape predation. We establish conditions for when the prey evolves toxicant resistance and for when this resistance may allow both the predator and prey to persist. Time permitting, we will also extend this model to consider evolution in response to disturbances that occur stochastically.

## Extinction Risk of a Metapopulation Under the Allee Effect

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We study the extinction risk of a fragmented population residing on a network of patches, where patches are coupled by diffusive migration and local patch dynamics include the Allee effect. We show that mixing between patches can either have a positive or negative effect on the population's viability, depending on the migration rate and flux between patches. In particular, weak migration is shown to always increase the population's global extinction risk, such that the population is better off being isolated rather than weakly mixed. This surprising result is in stark contrast to local logistic dynamics, where any nonzero migration rate decreases the population's extinction risk. In the regime of intermediate migration, we find that in some cases there exists a critical migration rate for which the extinction risk is maximized. Notably, as the migration rate further increases, we demonstrate the existence of an optimal migration rate for which the extinction risk is minimized. However, this non-monotonic dependence is parameter-dependent. In other cases, we reveal a markedly different behavior, where the extinction risk monotonically increases with the migration rate, indicating that even an arbitrarily-strong migration is insufficient to rescue the population. Our theoretical results are verified via highly-efficient numerical simulations based on the weighted ensemble method.

## NEW TOOLS FOR DESIGN AND ANALYSIS OF STOCHASTIC SINGLE-CELL EXPERIMENTS

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Modern single-cell experiments, such as single-molecule fluorescent in situ hybridization (sm-FISH), can measure the positions and numbers of individual mRNA in single cells. However, such experiments often have low throughputs, it is not clear what are the optimal conditions and times under which to conduct these experiments, and it is unknown what minimal optical microscopy capabilities are needed to apply these powerful experimental procedures. As a result, costly datasets taken at intuitively designed, yet potentially sub-optimal conditions, may be too small to constrain models using traditional methods that rely on the validity of the central limit theorem. Previously, we have shown that fitting the observed mRNA histograms with nonlinear statistical models computed by the finite state projection (FSP) algorithm can overcome this challenge to discover predictive models with tightly constrained parameters, even when using small datasets.

I will report our ongoing progress to improve the efficiency and broader applicability of FSP-based methods for the analysis and design of single-cell experiments. This includes the development of new numerical methods for parameter estimation and uncertainty quantification, using concepts and tools from other computational science and engineering fields such as model reduction and multi-fidelity analysis, as well as high-performance computing platforms. In addition, I will also discuss our recent work to extend the FSP analysis to compute a more accurate formulation of the Fisher Information Matrix (FIM). This advance, which we call the FSP-FIM, allows us to estimate the informative potential of a wide range of potential single-cell experiments in an effort to select those that provide the most information at the lowest cost. I will demonstrate how the FSP-FIM enables the design of optimal single-cell experiments in many contexts, including the design of environmental perturbations such as chemical or optogenetic inputs, the choice of optimal experimental measurement times at which to perform smFISH, and the specification of optimal initial conditions as can be achieved through fluorescence-activated cell sorting. We will also use the FSP-FIM to explore how different types of experimental measurement errors or different image processing inaccuracies can affect how much information can be extracted from single-cell experiments, and we will discuss how such analyses reveal new insight for the specific design requirements of single-cell optical microscopy.

# Immigration and Tuberculosis in Chile: A deterministic mathematical model

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The economic and political stability in Chile in the last years has been determinant for the growing immigration rates of the country. This mobility can provoke the appearance of diseases that are unknown in Chile, or can produce an increase in prevalence or incidence of diseases that have been controlled in the country. Tuberculosis (TB) is a bacterial disease transmitted from person to person through the air. In Chile, a slowdown in the decrease of TB prevalence has been observed during the last years. One of the risk groups are immigrants coming from countries with high TB prevalence compared to Chile. We present a deterministic mathematical model to describe TB dynamics in Chile. We analyze which factors related to immigration in Chile could affect TB prevalence and give recommendations on diseases control.

## **Options for Integrating Computational Modeling into Biological Curricula**

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At the turn of the millennium, systems biology forcefully began to move into the mainstream of biology. Initially advanced by only a relatively small number of practitioners, the concepts and methods of the field are now increasingly being demanded by biology students around the world, even at the undergraduate level. Because most biology students of the past had insufficient mathematical training to perform sophisticated computational modeling, the situation requires innovative solutions. Here we present three strategies we have taken in recent years to attract students to the emerging field of systems biology. One strategy consists of the incorporation of stand-alone, single-class modules into a large freshman undergraduate biology course. The first of these modules focused on homeostasis in the context of red blood cell dynamics. The second strategy focuses on modeling in direct association with wet experiments, where both wet and modeling experiments are performed by advanced undergraduates. For this purpose, we chose the uptake of antibiotics in plants, which is directly tied to metal uptake, although the mechanisms are not fully understood. The modeling uses differential equations within software that is relatively easy to understand and manipulate. It goes hand-in-hand with growth experiments using wild type and mutant plants, as well as different media and conditions. Finally, we have created an elective course that in its entirety focuses on one particular disease, which differs from year to year. As early as Week 1 or 2 of this course, students start working with a prefabricated model of some aspect of the disease and gradually learn modeling techniques and alternatives, as well as details of the disease. At about the half-point of the semester, the student self-organize into groups of two or three students. They design and implement their own models of some new aspects of the disease, repeatedly present their thinking and progress to the class, receive feedback from peers and instructors, and ultimately write a term paper about their model, which usually demonstrates that they feel empowered by the process and proud of their achievement.

## Of clocks and waves: *in silico* evolution of animal segmentation

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Segmentation is the developmental process which subdivides the main body axis into many repeated elements. In most arthropods and vertebrates, segments are produced one by one from a posterior undifferentiated zone, by a “clock-and-wavefront mechanism”: gene expression oscillations in the undifferentiated zone are turned into a striped segmental prepatter by a receding wavefront of morphogen.

In vertebrates, the gene regulatory network (GRN) causing the oscillations is highly complex, and so are the resulting gene expression dynamics; the oscillations gradually slow down before prepatter formation, generating the appearance of travelling waves in a long undifferentiated region. While such travelling waves have also been observed in some arthropod species, variation in the extent of these travelling waves exists in both the chordate and arthropod lineages. It is therefore unclear under what conditions travelling waves and network complexity are more likely to evolve, and whether they are related.

To investigate this, we use a previously developed computational model of the evolution of segmentation. We vary the extent of the posterior morphogen gradient in the *in silico* tissue and the level of gene expression noise in the gene expression dynamics. We find that populations evolve segmentation more easily and with simpler GRNs under a steep, short morphogen gradient compared to a shallow, long gradient. The oscillations evolved with a steep gradient are often damped, while oscillations evolved with a shallow gradient are usually persistent. Travelling waves are more likely to emerge when individuals have a shallow gradient and higher gene expression noise. However, the evolution of GRN complexity and travelling waves are not correlated, which suggests that they may have evolved independently.

Based on our findings, we suggest that travelling waves may have evolved in response to shallow morphogen gradients and gene expression noise. These two factors may thus also be responsible for the observed differences between different species within both the arthropod and chordate phyla.

## Dynamics of a non-smooth epidemic model with three thresholds

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A non-smooth epidemic model with piecewise incidence rate dependent on the derivative of the case number is proposed for the transmission dynamics of an infectious disease with media coverage, enhanced vaccination and treatment policy. This is an implicitly defined system, which is converted into an explicit system with three thresholds by employing the properties of the Lambert  $W$  function. We first analyze the dynamics of the proposed model for the limiting case, which induces two non-smooth but continuous models. The dynamic analysis of the proposed model exhibits one of two generalized equilibria or the pseudo-equilibria or the disease-free equilibrium is globally asymptotically stable if the disease does not die out. This suggests that the proportion of infected individuals can be contained at either an *a priori* level or at a high/low level, depending on the threshold, which governs whether the enhanced vaccination and treatment policies are implemented. Media coverage cannot help eradicate the disease, but it significantly delays the epidemic peak and lowers the peak proportion of infected individuals. Hence, a good threshold policy and continuously updating the awareness of case numbers are required to combat the disease successfully.

## The effects of delayed dispersal in ecological models

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In this talk, I will present some recent work on studying the effects of delayed dispersal in predator-prey metapopulation models and competition models. I will show that either the dispersal delay is harmless in the sense that it does not affect the stability of the metacommunity, or the dispersal delay can induce stability switches with finite number of stability intervals. I will also show that in some cases, the delayed dispersal can induce multiple coexistence equilibria and the dispersal has significant impacts on determining the competition outcome and can induce multi-stability.

# Modeling and assessing the effect of the movement of boars on the spread of African swine fever in China

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This paper is devoted to the transmission of African swine fever (ASF) between domestic boar populations and wild boar populations. A two-patch model is proposed to investigate how the movement of domestic boars and wild boars affects the spread of ASF. We introduce the basic reproduction number associated with the disease, and define new indexes to reflect the risk of domestic boars caused by one domestic boar or wild boar. The numerical result shows that wild boar migration is more harmful to disease outbreak than domestic boars migration, and the migration of boars may make the disease outbreak even if the disease dies out in each isolated patch when there is no migration. Moreover, it is from the new indexes that wild boar migration will increase the ASF transmission in domestic boar populations. Our results suggest that limiting the wild boar migration may help to reduce the of ASF virus in domestic boar populations.

## Turing patterns in a predator-prey model with seasonality

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Many ecological systems show striking non-homogeneous population distributions. Diffusion-driven instabilities are commonly studied as mechanisms of pattern formation in many fields of biology but only rarely in ecology, in part because some of the conditions seem quite restrictive for ecological systems. Seasonal variation is ubiquitous in temperate ecosystems, yet its effect on pattern formation has not yet been explored. We formulate and analyze an impulsive reaction-diffusion system for a resource and its consumer in a two-season environment. While the resource grows throughout the ‘summer’ season, the consumer reproduces only once per year. We derive conditions for diffusion-driven instability in the system, and we show that pattern formation is possible with a Beddington-DeAngelis functional response. More importantly, we find that a low over-winter survival probability for the resource enhances the propensity for pattern formation: diffusion-driven instability occurs even when the diffusion rates of prey and predator are comparable (although not when they are equal).

# A PREDATOR-PREY MODEL WITH SEASONALITY AND MATURATION DELAY: AN APPLICATION TO PHAGE-BACTERIA DYNAMICS

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**ABSTRACT** Coexistence and seasonal fluctuations of predator and prey populations are common and well documented in ecology. Under what conditions can predators coexist with prey in a seasonally changing environment? What factors cause seasonal oscillations of some predator and prey species? To answer these questions, we investigate an improved predator-prey model based on the Rosenzweig-MacArthur model. Our model incorporates seasonality and a predator maturation delay, leading to a system of periodic differential equations with a time delay. We define the basic reproduction ratio  $R_0$  and show that it is a threshold parameter determining whether the predators can coexist with the prey. We show that if  $R_0 < 1$ , then the prey population has seasonal variations and the predator population goes extinct. If  $R_0 > 1$ , then the prey and the predators coexist and fluctuate seasonally. As an example, we study a phage-bacteria system and explore possible mechanisms for seasonal population cycles. Our numerical simulations indicate that seasonal phage-bacteria cycles are attributed to seasonality rather than phage maturation delay or phage-bacteria interaction. In the absence of seasonal variations, the phage-bacteria interactions can produce non-seasonal fluctuations with a higher frequency. The maturation delay is found to affect the amplitude of cycles and average population levels.

## Complex bursting patterns in an embryonic respiratory neuron model

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Pre-Bötzinger complex (Pre-BötC) network activity within the mammalian brainstem controls the inspiratory phase of the respiratory rhythm. While bursting in pre-BötC neurons during postnatal period have been extensively studied, little is known regarding inspiratory pacemaker neurons at embryonic stages. Recent data in mouse embryo brainstem slices have revealed the existence of different intrinsic bursting activity patterns depending on distinct combinations of burst-generating  $I_{\text{NaP}}$  and  $I_{\text{CAN}}$  conductances. In this work, we consider a model of an isolated embryonic pre-BötC neuron with two independent bursting mechanisms. We use methods of dynamical systems theory, such as phase plane analysis, fast-slow decomposition, and bifurcation analysis to uncover mechanisms underlying three different types of intrinsic bursting patterns observed experimentally - plateauing, oscillatory, and mixed plateauing/oscillatory. Our analysis also elucidates how the balance of the two bursting mechanisms leads to changes in inspiratory pacemaker type composition during prenatal development.

## Large time solutions in Wanner-Gujer type biofilm models

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Since the mid 1980s, there have been many models of biofilm growth that are broadly based on that proposed by Wanner-Gujer in 1984. They describe the 1-D depth expansion of biofilms, and in their basic form account for birth and death of cells in response to a diffusible nutrient. The volume changes due to growth and death result with an internal velocity field, mathematically leading to coupled systems of hyperbolic PDEs and a typically non-zero velocity divergence. These models have been well studied numerically and analytically, but significantly less work has been undertaken on analysing the long-time solutions of these models. In this talk, a Wanner-Gujer type model will be presented accounting for quorum sensing mediated exo-polysaccharide production in a viscous biofilm. The steady-state (in the case of surface detachment) and travelling wave (intermediate growth phase) limits will be presented. The resulting reduced models provide an efficient means, using shooting methods, of determining numerically the effects of parameters (e.g. quorum sensing, biofilm material properties etc.) on biofilm measurables, e.g. steady-state thickness, surface growth rates and overall cell densities. There are numerical challenges, however, and these will also be discussed.

## **Impacts of photosynthetic parameter selection and acclimation on modeled tree carbon gain**

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Boreal forests are crucial in regulating global vegetation-atmosphere feedbacks, but the impact of climate change on boreal tree carbon fluxes is still unclear. Given the sensitivity of global vegetation models to photosynthetic and respiration parameters, we determined how predictions of net carbon gain (C-gain) respond to variation in these parameters using a stand-level model (MAESTRA). We also modelled how thermal acclimation of photosynthetic and respiratory temperature sensitivity alters predicted net C-gain responses to climate change. We modelled net C-gain of seven common boreal tree species under eight climate scenarios across a latitudinal gradient to capture a range of seasonal temperature conditions. Physiological parameter values were taken from the literature together with different approaches for thermally acclimating photosynthesis and respiration. At high latitudes, net C-gain was stimulated up to 400% by elevated temperatures and CO<sub>2</sub> in the autumn but suppressed at the lowest latitudes during midsummer under climate scenarios that included warming. Modelled net C-gain was more sensitive to photosynthetic capacity parameters than stomatal conductance or respiration parameters. The effect of photosynthetic thermal acclimation depended on the temperatures where it was applied: acclimation reduced net C-gain by 10%–15% within the temperature range where the equations were derived but decreased net C-gain by 175% at temperatures outside this range. Thermal acclimation of respiration had small, but positive, impacts on net C-gain. We show that model simulations are highly sensitive to variation in photosynthetic parameters and highlight the need to better understand the mechanisms and drivers underlying this variability (e.g., whether variability is environmentally and/or biologically driven) for further model improvement.

# Shining light on shadow enhancers' regulation of transcriptional dynamics and noise

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Developing organisms establish and maintain precise and robust patterns of gene expression critical for proper pattern formation. This is accomplished despite potential perturbations and the significant amount of noise inherent in transcription. Transcription is not a smooth and continuous process, but instead occurs in bursts of activity, owing to the stochastic nature of the underlying molecular interactions [1]. These bursts of transcriptional activity, separated by periods of relative silence, have important implications for cellular function, as mRNA levels and fluctuations largely dictate these quantities at the protein level [2]. Such fluctuations in regulatory proteins, like transcription factors and signaling molecules, can propagate down a gene regulatory network, significantly altering the expression levels or noise of downstream target genes [3]. This raises an important question of how organisms maintain precise and robust gene expression.

Prior work has addressed mechanisms to buffer noise such as temporal or spatial averaging [4,5] or the use of redundant transcription factors (TF) [6]. Another potential buffering mechanism is shadow enhancers, groups of two or more enhancers that drive overlapping expression patterns of the same target gene [7]. Shadow enhancers have been identified in a wide range of organisms and are critical for robust gene expression [8,9]. We have observed that there is a widespread use of different TFs by the different individual enhancers of a shadow enhancer group. We propose that this separation of inputs allows shadow enhancers to buffer noise and maintain stable levels of gene expression.

To test this, we measure transcriptional dynamics of the embryonic shadow enhancers of Krüppel, a key developmental transcription factor, in live *Drosophila* embryos using the MS2 reporter system. By tracking biallelic MS2 expression, we are able to compare enhancer activity in single nuclei and quantify total levels and sources of expression noise. In conjunction, we use experimental data to inform and constrain a simple model of shadow enhancer regulation of transcription. We find that the individual member enhancers of the shadow enhancer pair act largely independently and display significantly different transcriptional dynamics, i.e. burst frequency and size, from one another and from the shadow enhancer pair. We also find that the shadow enhancer pair drives lower total noise than duplicated enhancers through decreases in both extrinsic and intrinsic sources of noise. By fitting to a small subset of transcriptional parameters, our model is able to recapitulate the lower expression noise associated with the shadow enhancer pair. Further, we find that the shadow enhancer pair is uniquely able to maintain low levels of expression noise across a wide range of temperatures.

Our findings support the idea that shadow enhancers separate inputs to decrease noise in gene expression output and suggest that this noise suppression may underlie the observed requirement of shadow enhancers during environmental or genetic stress.

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## Modelling time since infection in mosquitoes: biting behaviour matters

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Models are increasingly being used to assess the potential for mosquito-borne pathogens to emerge in novel geographic regions. In particular, characterizing how temperature affects estimates of the basic reproductive number,  $R_0$ , is an important component of understanding the risk of transmission in a warming world. As we incorporate parameter dependence on temperature and other environmental variables into our predictions of  $R_0$ , we should also (re)consider the structural assumptions of the underlying model framework. Most models of mosquito-borne disease are derivatives of the Ross-Macdonald framework, which assumes that the age at which a mosquito becomes infected does not impact its ability to transmit the pathogen. In addition, a mosquito in such a model could, in theory, live infinitely long and bite infinitely much. In this talk, we discuss a framework that relaxes these assumptions by structuring the female adult mosquito population by the number of bites taken and incorporating a gamma-distributed extrinsic incubation period. We compare output from this model to those from models without biting structure and show that predictions of  $R_0$  are reduced. Consequently, fitting a model to match observed values of  $R_0$  without considering model structure may result in incorrect estimates of parameters. Using data on chikungunya virus, we also demonstrate that the predicted optimal temperature for viral transmission depends on model structure.

## Approach-Avoidance Conflict in Posttraumatic-Stress Disorder

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Posttraumatic stress disorder (PTSD) is characterized by alterations in both avoidance and approach systems, showing heightened avoidance of trauma reminders as well as impaired reward processing. Although these competing processes are well-known in PTSD, no prior research has investigated the conflict of approach and avoidance behavior in PTSD. The purpose of this study was to investigate approach and avoidance systems in PTSD using an approach-avoidance conflict task.

43 women with PTSD and 14 controls participated in Study 1, and 48 incarcerated women participated in Study 2. Trials were separated into conflict phases (the option most likely to win points was most likely to show a trauma-related image) and congruent phases (the option most likely to win points was least likely to show these images).

Study 1 revealed that participants with PTSD earned significantly fewer points later in the conflict phase compared to controls, consistent with heightened avoidance at the expense of obtaining reward ( $t=-2.7$ ,  $p=0.006$ ). Study 2 demonstrated an interaction between PTSD symptoms and phase; participants with higher PTSD symptoms earned fewer points during the conflict phase ( $t=2.9$ ,  $p=0.003$ ), but PTSD symptoms were not related to points earned during the congruent phase.

These results are the first to show a specific impairment in approach-avoidance conflict resolution in participants with heightened PTSD symptoms. These data suggest that the imbalance of these competing systems produces impairments in approach-avoidance conflict resolution in participants with PTSD, which could generalize to a general sacrifice of potential rewards in the presence of potential trauma reminders.

## Spatial Spread of Epidemic Diseases in Geographical Settings: Seasonal Influenza Epidemics in Puerto Rico

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Deterministic models are developed for the spatial spread of epidemic diseases in geographical settings. The models are focused on outbreaks that arise from a small number of infected hosts imported into subregions of the geographical settings. The goal is to understand how spatial heterogeneity influences the transmission dynamics of the susceptible and infected populations. The models consist of systems of partial differential equations with diffusion terms describing the spatial spread of the underlying microbial infectious agents. Applications are given to seasonal influenza epidemics in Puerto Rico.

## Modelling microtubule dynamic instability: microtubule growth, shortening and pausing

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Microtubules (MTs) are protein polymers found in all eukaryotic cells. They are crucial for many cellular processes including cell movement, cell differentiation, and cell division. In performing these functions, they go through random periods of relatively slow polymerization (growth), followed by very fast depolymerization, an event referred to as a catastrophe. This “slow” growth and “fast” shortening is unique to MTs, and is referred to as dynamic instability. Aside from growth and shortening, some experimental studies suggest that MTs may also undergo periods of pausing, and the reasons for this are largely unknown. Here, we propose a model for MT dynamics which accounts for growth, shortening, nucleation (the event that initiates formation of MTs), and MT pause. Using numerical simulations, we examine how the behavior of MTs change, depending on whether or not a pausing state is considered. We compare our results with the experimental literature.

## Using a Mathematical Model to Explore the Power of Systemic Inflammation in Tumour Growth

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Inflammation is known to be a powerful promotor of tumour growth that is difficult to measure and quantify *in vivo*. In this work, I describe our attempt to explore the inflammatory response through a simultaneous tumour-growth experiment. Experimental data demonstrates that simultaneous injection of cancer cells at two distinct sites often results in one large and one small tumor. We hypothesize that unbalanced inflammatory cell accumulation may be the cause of the growth rate separation. To test this, we develop a mathematical model for tumor growth with inflammation and competition between the two cancer sites. Using this predictive model, we explore the role of tumor-promoting inflammation in the observed growth rate differences. Due to the experimental setup, immune predation may be neglected, focusing the model on tumor-promoting immune actions only. The multi-compartment differential equation-based model is parameterized by fitting to the experimental data using a simulated annealing algorithm. Numerical simulations are used to explore potential mechanisms driving the growth rate separation of the two tumors. The model predicts that unbalanced inflammatory actions, and in particular, a pre-inflamed site, can cause the growth disparities observed in the experimental data. Importantly, no additional inhibitory mechanism is needed to explain the biological phenomenon.

## Mathematical models of leukemia development and treatment.

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The talk will discuss mathematical models of chronic lymphocytic leukemia (CLL). Various aspects of how CLL develops remain unclear. Cells that bear characteristics of CLL are found in the blood of healthy individuals, a condition called Monoclonal B-cell lymphocytosis (MBL). Such altered cells in healthy individuals can persist temporarily and disappear, or they can persist and put the patient at risk for CLL development. Mathematical models will be presented that explore these dynamics and suggest a way to predict whether MBL is a temporary condition or a persisting one. Further, mathematical models of CLL generation will be considered to examine the potential role of cancer stem cells in this disease. Finally, the talk will summarize mathematical work that characterizes treatment responses of CLL to tyrosine kinase inhibitors.

## An alternative formulation for a delayed logistic equation

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An alternative single species logistic distributed delay differential equation with decay-consistent delay in growth is derived. We prove that the model does not permit sustained oscillations and that when the delay is sufficiently long the population dies out. Such dynamics are more biologically realistic compared to the dynamics predicted by the classical delayed logistic model. We establish a threshold for survival and extinction: in the former case, it is confirmed using Lyapunov functionals that the population approaches the delay modified carrying capacity; in the later case the extinction is proved using the fluctuation lemma. We further use adaptive dynamics to conclude that the evolutionary trend is to make the mean delay in growth as short as possible. This confirms Hutchinson's conjecture and fits biological evidence.

## Local model of cancer subtypes identifies master regulators and destabilizers

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Current standard-of-care treats small-cell lung cancer (SCLC), a highly aggressive and deadly form of lung cancer, as a homogeneous disease. While treatment is initially efficacious, the disease inevitably relapses, refractory to further treatment. Recent work has uncovered heterogeneity within SCLC, primarily interpreted along a phenotypic axis spanning neuroendocrine and epithelial (NE) phenotypes toward mesenchymal-like (ML) phenotypes. Here we investigate two new hybrid SCLC phenotypes that show mixed, partial expression of both NE and ML markers. Significantly, one hybrid phenotype has increased drug resistance to a broad range of treatments, including the standard-of-care. Nevertheless, the mechanisms regulating these hybrid SCLC phenotypes are not well known. To understand their stability, we infer a transcription factor (TF) network regulating SCLC heterogeneity. To overcome the limited knowledge of global regulatory details within this network, we developed an approach that constrains the dynamics only locally, near steady-states where the available information is rich, while regions between steady-states are constrained by the network topology. *In silico* perturbations of the network identify master regulators and destabilizers of each SCLC phenotype that are robust to uncertainty in poorly constrained regions. Future validation of these master TFs may lead to improved treatments by destabilizing resistant phenotypes, and reinforcing sensitive phenotypes.

# A reaction-diffusion model of vector-borne disease with periodic delays

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A vector-borne disease is caused by a range of pathogens, and transmitted to hosts through vectors. To investigate the multiple effects of the spatial heterogeneity, the temperature sensitivity of extrinsic incubation period (EIP) and intrinsic incubation period (IIP), and the seasonality on disease transmission, we propose a nonlocal reaction-diffusion model of vector-borne disease with periodic delays. We introduce the basic reproduction number  $\mathfrak{R}_0$  for this model and then establish a threshold type result on its global dynamics in terms of  $\mathfrak{R}_0$ . In the case where all the coefficients are constants, we also prove the global attractivity of the positive constant steady state when  $\mathfrak{R}_0 > 1$ . Numerically, we study the malaria transmission in Maputo Province, Mozambique. This talk is based on a joint work with Prof. Xiaoqiang Zhao.

## Traveling Waves on Time-delayed Reaction Diffusion with Degenerate Diffusion

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In this talk, we will present our current research results on time-delayed reaction-diffusion equations with degenerate diffusion. For the time-delayed degenerate diffusion equations with nonlocality and without nonlocality, their characteristics are essentially different. For the nonlocal reaction-diffusion equations with degenerate diffusion and time-delay, the family of minimum wave speeds corresponding to all the degenerate diffusion coefficients is proved to admit a uniform positive infimum. However, in the local case, there is no positive infimum of all the minimum wave speeds. This difference indicates that the nonlocal effect plays a role as Laplacian such that a positive lower bound independent of the degenerate diffusion exists for the minimum wave speeds. The degeneracy of diffusion for the equation causes us essential difficulty in the proof. A number of numerical simulations are also carried out.

## Modeling Mitigating Strategies for Dengue Virus Transmission

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Dengue virus is mainly transmitted by *Aedes aegypti* and *Aedes albopictus*, leading to great economic cost and posing threat to people's health in many tropical and subtropical regions. In this talk, I present an ordinary differential equation model used to assess the effectiveness of mitigation strategies against dengue virus transmission. We proved the local and global stability of disease free equilibrium and endemic equilibrium. We derived the target reproduction number to measure the control efforts, and the effective reproduction number to quantify the number of secondary cases for partially susceptible populations. Sensitivity analysis showed the relative significance of the model parameters. We compared different scenarios of vaccination for humans, and proposed ten control schemes and the necessary conditions for an optimal control strategy using Pontryagin's maximum principle, and the optimal control schemes were illustrated by numerical simulations

## Patient-specific predictions *via* multi-scale imaging and multi-scale modeling

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We will present our ongoing efforts developing quantitative, time-resolved microscopy and magnetic resonance imaging (MRI) methods to calibrate predictive, patient-specific, mathematical models of tumor growth and treatment response in breast cancer. In particular, we will discuss: 1) model design and development, 2) integration of theory and experiment, and 3) clinical application. The immediate scientific goal is to provide a rigorous, but practical, experimental-computational approach describing tumor development informed and validated by observable, quantitative data. Success would allow us to reach the ultimate clinical goal of providing accurate predictions of response guide interventions, thereby improving patient outcomes.

We begin with a system of tissue scale, mechanics-coupled, reaction-diffusion equation that characterize tumor cell growth and invasion as well as vascular delivery of systemic therapeutics. This model is calibrated by patient-specific, quantitative MRI data that report on cellularity, tissue volume fractions, and vascularity and enables tissue segmentation within the computational domain. These data are acquired both before and early in the course of therapy to calibrate model parameters, thereby enabling predictions the spatiotemporal development of the tumor.

More recently, we have employed quantitative MRI data to constrain computational fluid dynamic simulations of tumor-associated blood supply and interstitial transport characteristics unique to each patient. This analysis is designed to improve our characterization of nutrient and drug delivery, as well as effects of interstitial flow on tumor growth and invasion. To the best of our knowledge, this is the first time that flow and pressure fields have been determined using only non-invasive, clinically available imaging data and established laws of fluid mechanics.

The model becomes multi-scale through a hybrid, cell scale approach that considers the tumor and endothelial cells as agents, while characterizing growth factor and nutrient distributions as continuous fields that impact the dynamics and stochastic phenotypic transitions of each cell. Data are provided by spatiotemporal measurements of proliferation, angiogenesis, and response to therapeutics in a 3D *in vitro* platform consisting of a collagen extracellular matrix in which cancer cells are cultured and through which an endothelialized functional blood vessel is integrated.

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# Dynamical equivalence for complex-balanced mass action systems

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Mass action kinetics, typically a nonlinear system of ODEs, is a common model for biological phenomenon. Often from some biochemical processes, one builds a labelled directed graph, from which an ODE system is defined. Dynamical properties can sometimes be deduced directly from the structure of the network. Mathematically, many networks (not only the one given by the biology) can give rise to the same ODE system, hence to the same dynamics. We call these systems *dynamically equivalent realizations*. We showed that whether a given system has a complex-balanced realization is a finite calculation. Moreover, we can utilize the freedom offered by dynamically equivalence to extend some classical results about complex-balanced systems.

## Time-dependent product-form Poisson distributions for reaction networks with non-linear dynamics

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**ABSTRACT:** It is well known that stochastically modeled reaction networks that are complex balanced admit a stationary distribution that is a product of Poisson distributions. In this talk, we consider the following related question: supposing that the initial distribution of a stochastically modeled reaction network is a product of Poissons, under what conditions will the distribution remain a product of Poissons for all time? By drawing inspiration from Crispin Gardiner's "Poisson representation" for the solution to the chemical master equation, we provide a necessary and sufficient condition for such a product-form distribution to hold for all time. Interestingly, the condition is a dynamical "complex-balancing" for only those the complexes that have multiplicity greater than or equal to two (i.e. the complexes that yield non-linear terms to the dynamics). We term this new condition the "dynamical and restricted complex balance" condition.

# Risk factors assessment for the spread of African Swine Fever in China using an extended Cox hazard model

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On 3 August 2018, African Swine Fever(ASF) was reported for the first time in a pig farm near Shenyang city in Liaoning province, China. Since then, it has been kept spreading since the first outbreak. The data of ASF outbreaks were collected by the China Animal Health and Epidemiology Center (CAHEC), and an extended Cox hazard model was performed to identify the risk factors associated with the hazard of a farm having ASF outbreak. The model results reveal that the farm which has sow and pig movement from other areas had 1.8 and 2.28 times greater hazard for having ASF outbreak, while the larger intensive farming (herd size >1000 heads) was associated with lower (74%) hazard of having ASF outbreak. The distance between the farms and the center of last outbreaks can influence the risk of ASF outbreak significantly, and its impact varies over time. The distance increased per 1% associated with 48% less hazard of the farm having ASF outbreak in the first two months (2-4 months, 63%; 4 months later, 42%). Identifying the risk factors and their risk level will enhance our understanding of the ASF outbreak in China, which may contribute to constructing risk-based surveillance strategies and controlling the ASF in China.

## The effect of movement behavior on population density in fragmented landscapes

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Landscape fragmentation arises from human activities and natural causes, and may create abrupt transitions (interfaces) in landscape quality. How landscape fragmentation affects ecosystems diversity and stability depends, among other things, on how individuals move through the landscape. In this work, we focus on the movement behavior at an interface between habitat patches of different quality. Specifically, we study how this individual-level behavior affects the steady state of a density of a diffusing and logistically growing population in two adjacent patches.

We consider a model for population dynamics in a habitat consisting of two homogeneous one-dimensional patches in a coupled ecological reaction diffusion equation. The movement between patches is incorporated into the interface conditions. We establish the existence, uniqueness, and global asymptotic stability of the steady state. Then we explore how the qualitative properties of the steady state depend on movement behavior.

We apply our analysis to a previous result where it was shown that a randomly diffusing population in a continuously varying habitat can exceed the carrying capacity at steady state. We clarify the role of nonrandom movement in this context. In particular, we determine conditions on movement rates and patch preference, so that the steady-state density exceeds the carrying capacity.

## The rise and fall of malignant clones under immune attack

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Cancer is an evolutionary process where somatic mutations interplay with the environment allowing for adaptation and drift. The role of the immune system has for long time been recognized in cancer, but whether tumors primarily grow by adapting to immune-mediated negative selection or by acquisition of immune-escape phenotypes remains an open question. In recent years, next generation sequencing technologies have allowed us to explore the imprinted signatures of positive and negative selection in the cancer genome. Here, we develop a stochastic model of cell growth and the acquisition of nonsynonymous and synonymous mutations. We determine the fate of cellular clones based on the phenotypes given by driver, passenger, deleterious, immunogenic and escape mutations and estimate the levels of selection under different scenarios. Thus, we are able to study the extent of immunoediting associated to negative selection of antigen-presenting clones versus acquisition of novel immuno-suppressive phenotypes. We applied our model to more than 500 CRC tumors from TCGA previously classified as hot or cold using pathology-based or RNA-seq based measurements. We compare the extent of immune-mediated negative selection using dN/dS of clonal versus subclonal neoantigens in immune-hot and immune-cold regions and validate the predictions of our model. We demonstrate that after immunoediting has reached the final stage (escape), cancer cells are no longer under negative selection and their dN/dS values converge towards neutrality.

## A First Generation Model of Stress and Metabolic Axis Interactions

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Some of the most pressing challenges in healthcare require a *dynamic* understanding of the cross-talk interactions between endocrine axes. For example, glucocorticoid hormones mediating the stress response are also important for glycemic control and are known to play a role in the development of metabolic conditions such as type 2 diabetes. While high-resolution continuous sampling techniques have revealed circadian and ultradian rhythmicity of stress hormones (e.g., cortisol), little is known about how these rhythms are decoded by peripheral tissues and endocrine organs, or how their dys-regulation leads to disease. In particular, the mechanisms by which hypercortisolism —either induced by chronic stress, medication or Cushing's syndrome— can lead to glucose intolerance and insulin resistance are not well understood.

To address this, we propose a mathematical model of glucose homeostasis that takes into account the antagonistic effects of glucocorticoids and insulin on GLUT transporters in peripheral tissues, as well as the effects of glucocorticoid pulsatility on insulin secretion. The model predicts differential dynamic responses following oral glucose tolerance tests in controls and subjects treated with the synthetic glucocorticoid dexamethasone. It also predicts a rhythmic behaviour of insulin and glucose, and explores how physiopathological changes in glucocorticoid dynamics (e.g., disrupted circadian rhythmicity, elevated baseline levels, abnormal stress response) may affect control mechanisms in the metabolic axis (e.g., insulin secretion and glucose uptake in peripheral tissue). In the long term, we envisage this class of mathematical models will guide experimental protocols that explore the effects of pulsatile vs continuous administration of glucocorticoids on islet function and glucose utilisation, ultimately uncovering the role of chronic stress on the onset of type 2 diabetes.

# Models to Assess the Effects of Wolbachia-carrying Mosquito Augmentations on the Control of Dengue

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The introduction of endosymbiont Wolbachia into laboratory-reared mosquito populations is an innovative new technology, which are then released to mix with natural populations to prevent the mosquito vectors from reproducing dengue virus or to suppress the density of natural mosquitoes and thus break the transmission cycle of dengue disease. Field trials of Wolbachia-carrying mosquitoes have now been implemented in many countries where there have been the outbreaks of dengue disease. Two stage-structured mathematical models are proposed to investigate the effects of non-identical sex ratio releases of Wolbachia-carrying mosquitoes and Wolbachia-carrying male releases with mating competition on the success of population replacement and suppression, respectively. The results showed that the success of population eradication will rely on assessing basic offspring number of natural mosquitoes, the selection of suitable Wolbachia strains and appropriate release amount of Wolbachia-carrying males. The results of this study will be helpful for public health authorities in designing proper strategies of mosquito augmentations for the control of dengue disease.

# A switch-like behavior in membrane-confined bimolecular reactions with respect to diffusivity and molecular reach

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Tethered enzymatic reactions are a key component in signaling transduction pathways. Many T cell receptors have long unstructured cytoplasmic tails that contain tyrosine sites serving as docking sites for cytosolic enzymes as well as regulating receptor activation when phosphorylated or dephosphorylated. To understand the role of the unstructured tails in regulating protein interactions when diffusion of receptors are confined within the cell membrane, we develop a particle-based stochastic reaction-diffusion model. The model suggests a switch-like behavior 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 then developed to approximate the more complicated multi-particle system, and used to explain how the switch-like behavior appears.

# Analysis of Keller-Segel Models with Logarithmic Sensitivity

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This talk is based on a series of recent works on the rigorous analysis of systems of hyperbolic-parabolic balance laws arising from Keller-Segel type chemotaxis models with logarithmic sensitivity. Results concerning the global dynamics, explicit decay rates, chemical diffusion limits and boundary layer formation of classical solutions in one and multiple space dimensions will be reported.

## Which head is ahead: Molecular motor dynamics in a microtubule bundle

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The transport of cell organelles to biologically-relevant locations in the cell cannot be efficiently accomplished by passive diffusion. Instead, cells rely on molecular motors moving along an ever-shifting network of polymers (microtubules) for targeted delivery. We present a stochastic model for a molecular motor stepping along an inhomogeneous bundle of microtubules, as well as a simplified analytical model that is easier to analyse. Using these models, we investigate how the preferred stepping direction of the motor (parallel or antiparallel to the microtubule growth, corresponding to kinesin and dynein motor families) quantitatively and qualitatively affects the cargo delivery. Based on our findings, we present some predictions on which motor type is responsible for which cargo type, given the experimental distribution of cargo in the cell; and report experimental findings which are consistent with this guideline for motor classification.

# Mathematical models for immune checkpoint blockades

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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 immune checkpoint receptors such as CTLA-4 and PD-1, expressed on the surfaces of all T cells, inhibit T-cell proliferation and function. These receptors can be blocked by antibody drugs, which pave the way for an anti-tumour immune response. We present several mathematical models on tumour-immune dynamics in the presence of checkpoint blockade therapy and discuss their clinical implications.

## Seasonal changes in habitat size and locations: population dynamics and dispersal strategies

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**Abstract:** In this talk, I will present the results from two models about a single-species population whose habitat is affected by seasonal changes. From the first model, we assumed the dispersal of the population is the same in different seasons, and studied the effect of seasonal change in habitat size on the population dynamics. In the second model, we focused on the dispersal strategy of the population and used an adaptive dynamics framework to examine the ideal free dispersal strategies in a seasonal setting.

## Abstracts - Contributed Talks and Posters

**A New Approach to Substrate Flux Approximation for Monod Boundary Value Problem  
Arises in the Study of Biofilms**

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We present an analytical approximation for the diffusive flux of a substrate into a reactive layer, in which the substrate is degraded according to Monod kinetics. This problem is described by a nonlinear two-point boundary value problem. The approximation is derived from Modified Adomian Decomposition Approach for boundary value problems and verified computationally, by comparison against a numerical solution of the problem. The analytical approximation is easy to evaluate and depends only on model parameters. It is shown that the approximation simplifies the study of biofilm reactor model arises in the waste water engineering.

# Model&data-based prediction of invasive species dynamics

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**Keywords:** Bayesian model-averaging, *partial differential equations*, spatio-temporal population dynamics, *Xylella fastidiosa*

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## Abstract

Partial differential equations (PDE) have proven to be an effective means of understanding spatio-temporal population dynamics. Various structures of PDE are likely to be considered as candidate models for a given ecological phenomenon. However, a decision has to be taken on how to make best use of all the various predictions that can be drawn from a family of models. In this talk, we propose using the PDE-based Bayesian model-averaging (BMA) approach to account for model and parameter uncertainties. Hence, we combine several competing spatio-temporal models of propagation for inferring parameters and drawing a consensual prediction of certain quantities of interest. This study is applied (i) to date and localize the invasion of *Xylella fastidiosa*, bacterium detected in Southern Corsica in 2015, France using post-introduction data, and (ii) to predict its future extent.

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## Capturing variability of tumor-induced mass-effect in glioma growth models

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Glioblastoma (GBM) is the most frequent malignant brain tumor in adults. Its invasive growth is frequently modeled as reaction-diffusion process that results in growth phenotypes classified on a spectrum between *nodal* and *diffuse* growth. GBM patients also present with varying amounts of *mass-effect*, tumor-induced tissue deformation and associated mechanical stresses in the tissue. Elevated solid stress in brain tumors is linked to neuronal loss and neurological dysfunction, affects the tumor environment and may contribute to tumor progression.

This suggests that the propensity of an individual tumor to displace healthy tissue can provide information about the tumor micro-environment and might be of predictive value for treatment and outcome. However, tumors of similar imaging volumes have been observed to give rise to different amounts of tumor mass-effect, possibly resulting in distinct mechanical stress distributions and magnitudes.

An open question is whether this variability in tumor mass-effect can be explained by common growth characteristics, such as the tumor's *proliferative* and *invasive* potential.

We investigate this question using a spatial model of mechanically-coupled tumor growth that includes the tumor's *displacive* potential as distinct growth characteristic. Invasive glioma growth is represented as a reaction-diffusion process. To simulate the tissue-displacing mass-effect, we model the growth domain as an elastic continuum in which the actual deformation of a tissue element is given by the combination of growth-induced strains and strains associated with the elastic response of the tissue. The model assumes a linear constitutive relation between mechanical stress and strain, and postulates a linear isotropic coupling between tumor cell concentration and growth-induced strain to represent the displacive potential of the tumor.

We present evidence from quantitative analysis of tumor mass-effect on clinical imaging data, and discuss findings from parametric studies of our mechanically-coupled tumor growth model.

# Predicting resilience profiles of the run-up to regime shifts in nearly-1D systems

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The forecasting of sudden, irreversible shifts in natural systems is a challenge of great importance, whose realisation could allow pre-emptive action to be taken to avoid or mitigate catastrophic transitions, or to help systems adapt to them. In recent years much progress has been made in the development of such early warning signals. However, much of the current toolbox is based around the tracking of statistical trends and therefore fails to provide concrete predictions of the timescales of transitions or resilience loss. Metric-based indicators are also difficult to implement when systems have inherent oscillations which can dominate the indicator statistics. To resolve these gaps in the toolbox, we can use additional system properties to fit parsimonious models to dynamics in order to predict transitions. Here we consider nearly-one-dimensional systems—higher dimensional systems whose dynamics can be accurately captured by one-dimensional discrete time maps—and show how the nearly-1D dynamics can be used to produce model-based indicators for critical transitions which produce concrete forecasts of the resilience and the time of transitions in the system. A particularly promising feature of this approach is that it allows us to construct early warning signals even for critical transitions of chaotic systems. We demonstrate this approach on two model systems: phosphorous recycling in a shallow lake, and an overcompensatory fish population.

## **A pandemic tool for emerging disease monitoring: Ebola as a case study**

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### **Abstract:**

Re-emerging and emerging infectious diseases have been identified as a challenge to global health. These diseases re-emerge with different characteristics and possible virulent that are unexpected. A typical example is the Ebola epidemic of 2014 that the associated high disease mortality could have been minimized if adequate preparedness has been implemented before its outbreak. Hence, there is a need for adequate surveillance and control measures that are adjustable to the real-time dynamics of the disease under consideration.

In this study, we developed a meta-population model of disease spread for 200 countries using some of the standard compartmental models of disease spread. A typical consideration is given to Ebola due to its high case fatality and the event of 2014. Using country-specific and air-flight data, and adjusting for land movement between neighboring countries, different control scenarios are evaluated. The modelling work is implemented on both javascript and R shiny where decision makers can adjust key disease parameters and evaluate their impacts. With this tool, an effective disease control strategy can be adopted.

### **Subdiscipline area:**

Mathematical epidemiology

## Stability analysis in prey predator model using BeddingtonDeAngelis functional response.

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We study preypredator model of plankton. This model has interaction terms, which represent a plankton dynamics that includes infochemical mediated trophic interactions. We consider a simplified two species model which has the DeAngelis-Beddington functional response, to describe the grazing pressure of microzooplankton (M) on phytoplankton (P) is controlled through external infochemical (C) mediated predation by copepods (Z). The Beddington DeAngelis functional response can be used to explain the predators per capita feeding rates on prey. This functional response can to describe mutual interference by predators within the ecosystem. In relation to this, the concept was used to highlight the effect of changes in prey density on the predator density attached per unit time. Further investigation found that in plankton models, the Beddington DeAngelis functional response can be used to perform a detailed mathematical analysis of the intra-specific competition among predators. Global stability analysis of two different prey-predator models is established and compared the system dynamics in relation to this. We found consistency between the two models using numerical and analytical approaches to identify the similarity and some minor differences.

## A two species model to study the transmission and persistence of MERS-COV

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Middle East Respiratory Syndrome coronavirus (MERS-COV) is a severe respiratory disease that has caused great burden in Saudi Arabia (KSA), among other countries. MERS-COV is carried by camels, and contact with infected camels is the main cause of this infection in humans. We have developed mathematical models of MERS-COV spread in KSA including the human-camel interface, using metapopulation and network modelling frameworks. We found the global stability for disease-free steady state and endemic steady state using Lyapunov function. The inquiry of our study showed a high prevalence of 70 - 75% Camels confirmed cases corresponding to 1728 patients with a mortality rate of 36%. The pairwise approximation models are derived from the exact probabilistic models, and mean-field approximations for homogenous and heterogeneous networks have been analyzed.

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## Continuous Model of Dynamic Instability of Microtubules with Pausing

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Microtubules (MTs) are protein polymers found in all eukaryotic cells. They are crucial for normal cell development, providing structural support for the cell and aiding in the transportation of proteins and organelles. In order to perform these functions, MTs go through random periods of relatively slow polymerization (growth) and very fast depolymerization (shrinkage), a unique type of dynamics called dynamic instability. The onset of a MT shortening event is called a catastrophe, while the event at which a MT starts to grow again is called a rescue. Although MT dynamic instability has traditionally been described solely in terms of growth and shortening, MTs have also been shown to pause for extended periods of time. Here, we present a novel mathematical model to describe dynamic instability in terms of growth, shortening and pausing. Our overall goal is to use this model to determine MT catastrophe and rescue rates, quantities that can be used to compare our model results with experimental findings.

Keywords: Microtubules, Nucleation, Catastrophe, Rescue, Pausing, GTP (Guanosine triphosphate) is hydrolyzed into GDP (Guanosine diphosphate)

Subdiscipline area : Mathematical Oncology

## Modeling the evolution of ploidy in a resource restricted environment

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Most gliomas are diagnosed as either lower-grade lesions (grade II) or Glioblastoma (grade IV). Progression of lower-grade gliomas (LGG) to Glioblastoma (GBM) is accompanied by a phenotypic switch to an invasive cell phenotype. Converging evidence from colorectal-, breast-, and lung- cancers, suggests a strong enrichment of high ploidy cells among metastatic lesions as compared to the primary. Even in normal development: trophoblast giant cells are responsible for invading the placenta during embryogenesis and strikingly these cells can have up to 1000 copies of the genome (Hannibal et al., 2014). All this points to the existence of a ubiquitous mechanism that links high DNA content to an invasive phenotype. We formulate a mechanistic Grow-or-go model that postulates higher energy demands of high-ploidy cells as a driver of invasive behavior.

The unit we are modeling is a cell, that comes with a certain ploidy, proliferation-, and death-rate. Variations in ploidy emerge as a result of chromosome missegregations. For each cell we calculate the probability of the cell to divide as a function of energy availability in its neighborhood vs. ploidy-dependent energy demand of the cell. This comparison between available and required energy is a surrogate for the dual role of integrin signaling: integrin-mediated signals allow cells to progress from G1 to S phase. At the same time integrins mediate cell migration. The model was implemented as a cellular automaton and 2,500 simulations were ran at variable energies and missegregation rates. In low-energy environments high-ploidy clones were enriched at the leading edge of the tumor. This was not the case in high-energy environments. Future validation experiments will compare the size and staining intensity of nuclei between regions annotated as cellular tumor vs. leading tumor edge as surrogates of differential ploidy (Puchalski et al., 2018). As a second line of validation we will expose GBM cell lines to different flow speeds and use the corresponding response of the fixation probability of high-ploidy clones as an indicator for model selection.

CNVs are a phenotypically effective form of genomic instability, leading to changes in the expression of a lot of genes simultaneously, even affecting the size of the cell. Our model proposes CNVs as an efficient route for cells to switch back and forth between migration and proliferation. This mechanism may contribute to the quick recurrence of GBMs after surgery and may also explain striking differences in the prognostic power of integrin signaling and cell cycle progression between males and females.

## Elite control of HIV exhibits some robustness properties

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The Human Immunodeficiency Virus (HIV) declines to undetectable levels in the peripheral blood after primary infection in a small number of untreated individuals over a period of several years. This phenomenon is known as *elite control* of HIV infection. It is important to improve understanding of elite control of HIV to inform the design of treatment strategies to sustain the decline of HIV load to undetectable levels after vaccine or antiretroviral therapy. We investigated how elite control of HIV sustains the decline of viral load using a mathematical model of HIV infection. This model describes the HIV infection of target cells, the generation of latently and productively infected cells, the activation of latently infected cells, the production of HIV free virion, the proliferation of the HIV-specific cytotoxic T cells which kill productively infected cells and the inhibition of this immune response by HIV. Control analysis of this model reveals a reachability condition must be satisfied to achieve elite control of HIV. This reachability condition describes analytically immunological requirements for sustaining the decline of HIV load as well as for reducing the population of productively infected cells to zero. The cytotoxic T cell response achieves elite control of HIV when the magnitude of the killing action is sufficient to satisfy the given reachability condition. As long as the reachability condition is satisfied, this elite killing sustains the decline of HIV load despite uncertainties and variations in biological rates and processes such as the generation of productively infected cells and activation of latently infected cells. Together, these results suggest that elite control of HIV exhibits some robustness properties.

## Stochastic SEIR Dynamics on an Edge-based Network Model

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This presentation studies the spread of an infectious disease wherein transmission occurs not according to a homogeneous mix, but according to the more realistic assumption that members of a population have heterogeneous contact rates. Thus, a network is used to track the infection dynamics. In particular, we study a disease with an incubation period to extend already known results for SIR models. An SEIR model is set up on a static network using an arbitrary degree distribution. The reproduction number and final size of the epidemic are derived. Stochastic simulations are performed using Gillespie's algorithm given Poisson and power-law distributions. Further numerical simulations are executed to explore variations in the disease parameters.

SUBDISCIPLINE AREA: Mathematical Epidemiology

## Analysis of cancer dynamics in fluctuating environments

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Solid tumours are complex ecosystems that exhibit both spatial and temporal heterogeneity. In particular, tumour vasculature is highly irregular and constantly re-modelled, giving rise to temporal variations in the level of vital nutrients, metabolites, and drugs. Such environmental variability requires cells to adapt, and has been hypothesised to select for more aggressive, drug-resistant, cancer phenotypes. In fact, risk spreading through spontaneous phenotypic variations (i.e. bet-hedging) is a known concept in ecology which is used to explain how species may survive in temporally varying environments (i.e. risk). This allows individuals within a species to diversify their phenotypes ensuring that at least some of them can survive in the face of sudden environmental change. We aim to investigate whether cancer cells may adopt this strategy when dealing with rapidly changing levels of nutrient due to temporally-varying blood flow.

With this aim, we consider a system of nonlocal partial differential equations modelling the evolutionary dynamics of two competing phenotype-structured cell populations in periodically-fluctuating environments. The phenotypic state of each cell is represented by a continuous variable, and the phenotypic landscape of the populations evolves in time due to variations in the level of nutrient. In order to assess the evolutionary role played by risk spreading, we consider the case where the two cell populations undergo spontaneous phenotypic variations with different probabilities. Exploiting the analytical tractability of our model, we study the long-time behaviour of the solutions to obtain a detailed mathematical depiction of evolutionary dynamics. The results obtained suggest that when nutrient levels undergo small and slow oscillations, it is evolutionary more convenient to rarely undergo spontaneous phenotypic variations. Conversely, under relatively large and fast periodic oscillations in the nutrient level, which bring about alternating cycles of starvation and nutrient abundance, higher rates of spontaneous phenotypic variations represent a competitive advantage. We discuss the implications of our results in the context of cancer metabolism.

## Measles: insights into waning immunity

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Measles is a vaccine preventable childhood infectious disease. However, every year new outbreaks are reported all over the world, even in countries achieving vaccination coverage levels at or above the target coverage of 95% [1]. It has been indicated that a cause of these cases may be related to the waning of vaccine-induced immunity [2,3]. We explore this using mathematical compartmental models (following *SIRV* framework with waning) describing measles dynamics and changes in immune status of individuals in a population, with and without age structure. Since the level of infectiousness of individuals that have waning vaccine-induced immunity is unknown, we vary this assumption in our studies. For the given model structure, we have derived the basic and control reproduction numbers ( $\mathcal{R}_0$  and  $\mathcal{R}_c$ ). We have also investigated how  $\mathcal{R}_c$  is affected by changes in  $\mathcal{R}_0$ , waning rates and the infectiousness of vaccinated individuals. Extending our study to a stochastic modelling framework, we have also quantified the probability of measles outbreaks in populations with specific  $\mathcal{R}_c$ , and vaccine coverage and waning immunity rates. Briefly, we find that waning vaccine-induced immunity against measles can render measles elimination impossible. However, we also find that the probability of outbreak in highly vaccinated populations can be almost zero - meaning that elimination can be observed.

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## Tracking unstable states: A complicated dance in a changing world

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Regime shifts and their significant implications for conservation are well known in diverse ecosystems. They have typically been described as shifts between alternative stable states. Here we show that ecological systems exhibit unforeseen shifts through the tracking of the unstable states under global environmental change. Indeed, regime shifts are strongly influenced by the rate of change of bifurcation parameters in the vicinity of critical points, and can result in the tracking of unstable states before shifting to actual stable state. We show that the slow response of individual state variables, and their interactions enable the tracking of unstable states: slow responses can lead to tracking of unstable state only in the transient phase, whereas even slower responses allow for tracking of only unstable states. Moreover, regime shifts associated with tracking of unstable states are observed at multiple critical bifurcation points, including unstable limit cycles. Our results show how the rate of climate change can be an important predictor of ecosystem response away from their stable state.

# A Mathematical Model for Cholera Transmission: Most Effective Control Strategy

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Cholera, an acute gastro-intestinal infection and an endemic disease around the world. It is the major cause of the child death in developing countries due to lack a heightened sense of hygiene and access to safe drinking water. In this work, we proposed a mathematical model which is describe the 2008 Cholera outbreak in Zimbabwe, for the transmission of *Vibrio cholerae* (Cholera) disease considering public health educational program or media alert and awareness program, vaccination, water sanitation and drug treatment as control strategies to eradication of disease. Mainly, we aim to give a better understanding of the effects of control measures coupled with the transmission dynamics of Cholera and this will in diverse ways help gain practicable and efficient preventive strategies for the control of the Cholera epidemic. The steady states (equilibrium points) and their stability are analyzed. We show that the disease-free equilibrium point is locally and globally asymptotically stable under the certain conditions on the parameters which is used in the proposed model. This means we can say that the Cholera can be removed under suitable condition on parameters. We analyze the mathematical model by obtaining the basic reproduction number with single and various combination of control strategy and compared with each other to determine the most effective combination of control. Sensitivity analysis of the parameters to basic reproduction number, of the model in the control of the Cholera epidemic will be established. Finally, we show some numerical simulation to support the analytical results. our results provide some new insights about the effective control strategy to eradication of Cholera.

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## **P-glycoprotein (Abcb1) expression and activity are sex-, feeding-, and circadian time-dependent, implications for mechanistic pharmacokinetics modeling.**

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P-glycoprotein (*P-gp*) is a main efflux transporter that mediates the detoxification of many anticancer drugs and other xenobiotics. Both *P-gp* expression and toxicities of *P-gp* substrates may largely vary according to the patient's sex, feeding status, and circadian timing system that rhythmically regulates the organism over 24h. A molecular understanding of inter- and intra-patient variations of *P-gp* activity would allow for optimizing drug exposure through personalized administration schedules. A systems pharmacology approach enabled us to simultaneously study the effect of sex, feeding status and circadian time on *P-gp* activity in the gastro-intestinal system of mice. Robust circadian changes in *P-gp* mRNA and protein levels were demonstrated in the ileum of mice of both sexes, with larger amplitudes and earlier phases in females as compared to males. In the colon, no circadian rhythm was found in *P-gp* mRNA amounts whereas protein levels only displayed time-dependent variations in females. Similarly, liver *P-gp* protein expression showed 24h-rhythm in females, but not in males. *P-gp* activity was assessed through multi-factorial PK studies of talinolol, a pure *P-gp* substrate. Statistically significant differences were found in plasma, ileum and liver talinolol PK profiles according to sex, feeding status and circadian timing. Physiologically-based modelling revealed that *P-gp* activity circadian mean was higher in males compared to females in both ileum and liver, for all feeding conditions. *P-gp* activity circadian amplitudes were consistently higher in females than in males. *P-gp* activity circadian maxima significantly varied with respect to sex by up to 10h. Fasting increased *P-gp* activity in both liver and ileum of male mice, and only in ileum of females, and decreased *P-gp* activity circadian amplitudes. The mathematical model of *P-gp* circadian activity that was developed in the gastro-intestinal system provided parameter estimates according to sex and feeding status. It can further be incorporated into physiologically based PK models of any *P-gp* substrates for personalizing their circadian administration.

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Title : An application of spatial stochastic interacting systems on multiple time scales to biological systems

Abstract :

His research deals with biochemical reaction network allowing gene expression. Each gene contains information required for a protein synthesis, but the expression of this information follows the same two-stage process. First of all, the DNA of the gene is transcribed into messenger RNA (mRNA) by RNA polymerase, then the mRNA is translated into protein by ribosomes.

We model this reaction network by a stochastic process in the space: each species (ARN or protein) moves in space over time and a transition rate is linked with each biochemical reaction. It stands for the probability that this reaction happened, and it depends on different parameters (distances between reagents, local quantity of reagents....).

Several cases are studied : movement more or less fast of molecules and autoregulation of protein number on mRNA's creation. The goal is to compare molecules' movement over time from case to case. By using simulations, we would illustrate the evolution of molecule's amount and the molecule's diffusion around space. We would show too asymptotic results in order to have information on behaviour in long time and on evolution over time of expectation and variance of molecule's amount.

## Marine Metapopulation: Pelagic larval duration and ocean currents mediated effects of climate change

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With ongoing rapid climate change, most marine benthic invertebrates and few territorial vertebrate fish species characterized by sedentary adult phase and larval pelagic phase are subjected to effects that increase adult mortality, modify pelagic features such as larval duration as well as ocean currents. Most ecological studies focus on direct and local impacts of climate change factors on survival and development of species and none have considered the indirect effects of both abiotic ocean currents and temperature-prone larval duration. In this study, we investigate the combined effects of climate change on both local mortality and regional dispersal and how they affect stability of marine metapopulations. We adopt the density-dependent metapopulation model of Bani et al., 2018 to develop a framework that predicts potential changes and effects of adult mortality and dynamic connectivity on marine metapopulation stability. Then tested the proposed framework using biophysical connectivity simulated during two time periods; actual (1998-2007) and future (2068-2077), in combinations with scenarios of adult mortality increase and larval duration reduction. Our results revealed how climate change induced changes of abiotic ocean currents and biotic larval duration interact in complex and opposing directions to shape dynamic connectivity-related processes which in return contribute non-additively to regional stability of marine metapopulation. Moreover, the impact of climate change varies along the whole larval duration spectrum, while the effects on species with short larval duration are mediated by temperature-prone larval duration, the effects on species with longer larval duration are mediated by physical ocean currents variability.

## Effects of clot contraction and fiber distribution on blood clot degradation

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Blood clots are composed of red blood cells and platelets held together by a mesh of fibrin fibers. When a blood clot blocks an artery to the brain, blood flow is severely reduced and ischemic stroke can occur. As stroke is a leading cause of disability and death in the United States, it is imperative to understand how blood clots degrade, and how to effectively treat a patient experiencing ischemic stroke, especially because current treatment modalities are inadequate. The conditions in which a clot forms can have a large impact on the clot structure, and hence on the clot degradability. In this talk we explore how degradation is affected by clot contraction and fibrin fiber distribution. We modify our previously-published three-dimensional multiscale model of clot degradation to include red blood cells. We calculate the rates and patterns of fibrin degradation and the spatiotemporal distribution of important enzymes in five different clots with realistic structures (obtained from laboratory experimentation). Experimental and model clots are uncontracted (red blood cells are distributed somewhat uniformly throughout the clot volume) or contracted (red blood cells are tightly packed and total clot volume is reduced). Additionally, fibrin fibers are distributed evenly inside and outside the region containing red blood cells, or a higher percentage of fibrin is located at the clot edge, outside the region containing red blood cells. We use our model to understand how these different types of clots degrade, and use the results to suggest targets for stroke treatment.

Subdiscipline area: Immunobiology and Infection

## SMB 2019 Contributed Talk Abstract

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TITLE: Computational modeling of macrophage polarization dynamics during bone healing

Myeloid-derived macrophages are abundant in bone and polarize into pro- and anti-inflammatory phenotypes, regulating bone injury repair mediated by osteoclasts and osteoblasts. Surprisingly, little is known of their polarization states and temporal dynamics during the repair process; a gap in our knowledge that is difficult to address with traditional biological approaches. In order to understand better these complex cellular interactions, we integrate empirical and published data on macrophage polarization states during bone healing into an ordinary differential equation (ODE)-based model. To this end, intratibial injuries were performed on C57BL/6 mice and bone marrows flushes were profiled by FACS analysis at days 0, 1, 2, 3, 7 and 14 ( $n=5$ /time point) for pro- and anti-inflammatory myeloid content (CD11b, Ly-6G, Ly-6C, NOS2 and ARG1). Contralateral tibias were collected at the same time points histologically assessed for bone volume ( $\mu$ CT), osteoblast (Runx2), and osteoclast (TRAcP) numbers. The collected data was used to power ODE-based population models. The model captures dynamic shifts in macrophage phenotypes during bone repair and their interaction with osteoclasts and osteoblasts, in agreement with the biological data. Interestingly, the model sheds light on the sources of pro-and anti-inflammatory macrophages, and suggests that osteoblast and osteoclast bone formation and resorption rates change over the course of injury. Having generated a model that takes into account macrophage dynamics during bone injury repair, we tested whether altering macrophage polarization could impact time to bone healing. Our ODE model of bone repair predicts that increasing pro-inflammatory macrophage population during the initial stages of injury, substantially decreases the time taken to repair and restore bone volume to homeostatic levels. The model captures pro- and anti-inflammatory populations modulation of osteoblast and osteoclast activity. It is being used currently to predict how macrophage targeted therapies can accelerate bone healing and how cells of the bone ecosystem, including macrophages, interact with cancer cells during metastatic seeding.

## Analyzing Dynamic Decision Models Using Differential Chapman-Kolmogorov Equations

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In a constantly changing world, decision making requires adaptive evidence accumulation that discounts old evidence and favors recent observations. To help understand the strategies used by different organisms, we used Bayesian methods to model how an ideal observer accumulates evidence in stochastically changing environments. We focused on two-alternative forced-choice tasks in which an observer makes decisions based on noisy observations of a state  $s(t) \in s_{\pm}$  of a continuous time Markov process with switching rate  $h$ . The continuum limit of these models are stochastic differential equations with nonlinear evidence discounting, or leak, describing an *ideal observer's belief*  $y$ :

$$dy = \underbrace{g(t)dt}_{\text{drift}} - \underbrace{2h \sinh(y)dt}_{\text{discounting}} + \underbrace{\rho dW_t}_{\text{noise}}$$

To efficiently characterize belief in tasks with both observation noise and stochastic switching, we derived differential Chapman-Kolmogorov (CK) equations for the observer's belief distribution conditioned on state  $s(t)$ ,  $p_{\pm}(y, t)$ . These coupled drift-jump-diffusion equations are parameterized by a single free parameter,  $m$ , representing *evidence strength*:

$$\frac{\partial p_{\pm}}{\partial t} = \underbrace{\mp m \frac{\partial p_{\pm}}{\partial y}}_{\text{drift}} + \underbrace{2h \frac{\partial}{\partial y} [\sinh(y)p_{\pm}]}_{\text{discounting}} + \underbrace{m \frac{\partial^2 p_{\pm}}{\partial y^2}}_{\text{diffusion}} + \underbrace{h [p_{\mp} - p_{\pm}]}_{\text{switching}}.$$

The resulting density can be integrated to determine the probability of a correct response. Varying task parameters shows that the nonlinear model is most sensitive to mistuning at intermediate task difficulties.

Our method is flexible and can be extended to study sub-optimal heuristic models, including those with linear or cubic evidence discounting and those with no-flux boundaries in place of evidence discounting; these models may describe the strategies organisms use, and can be tuned to have accuracy nearly identical to the ideal observer model. However, we show that these approximate models are also more sensitive to changes in their evidence discounting parameters than the nonlinear model. We can further extend our method to models with additional internal noise, and to tasks where evidence is obtained in discrete pulses. Increasing internal noise requires smaller discounting rates, and hence longer integration times, to maximize observer accuracy. Our methods allow us to efficiently study how different decision strategies result in trade-offs between accuracy and complexity, as well as between variability and bias.

## Evolutionary tempo and the tumor microenvironment

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Cancer progression and evolution is driven by genetic mutations but also by the selection resulting from the interactions between the tumor, stromal cells and the environment. This picture is further complicated by the fact that tumors are characterized by genetic and epigenetic heterogeneity, one of the most basic of them being the distinction between stem-like and the rest of the tumor cells. In this talk we show a computational agent-based tumor model, assuming proliferative hierarchy and heterogeneous oxygen availability distribution. Computational predictions are compared with clinical data derived from histologic samples taken from glioblastoma patients at the Moffitt Cancer Center. These were stained to elucidate areas of hypoxia and necrosis, and to identify p53 expression heterogeneity. Hypoxia-driven evolutionary dynamics select for tumor-initiating clonogenic cells in low oxygen regions which could impact the efficacy of known treatments. We contrast these results with previous theoretical work that stated the importance of transient cell proliferative potential in limiting overall tumor growth and show how hypoxia can overcome that limitation and promote tumor clonogenicity. A key finding is that these hypoxic regions could be altering the evolutionary tempo and drive the increase in mutations which could fuel tumor heterogeneity. Implications of this for tumor evolution and treatment are discussed.

# **USING MATHEMATICAL MODEL TO ASSESS THE IMPACT OF VACCINATION OF MEASLES**

**By**

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**And**

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## **Abstract**

*This paper presents mathematical model to investigate the declination of measles due to vaccination. The primary aim of this study is to increase global understanding and ability to prevent death and illness due to measles. We employed an SEVIR model which includes; susceptible, exposed, vaccinated, infected and recovered compartments. Stability analysis for Disease Free Equilibrium and Epidemic Equilibrium have been carried out to evaluate the impact of the vaccination method of control. We finally recommended that Immunization organisations in collaboration with government ought to reinforce routine vaccination system and effort should be intensified towards decreasing the level of contact rate.*

**Key words:** compartments, Epidemic, stability analysis, Disease free Equilibrium

# Pushing Boundaries: The existence of solutions for a free boundary problem modelling the spread of ecosystem engineers

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Modeling the movement and spread of invasive species into a new environment has been the subject of many publications in population ecology. The overwhelming majority of models for spreading populations are based on Fisher's reaction-diffusion equation. This approach assumes that the habitat quality is independent of the population. Ecosystem engineers are species that modify their environment in order to make it (more) suitable for them. Beavers are a well-known engineering species. A potentially more suitable modelling approach in this case is to adapt the well-known Stefan problem of melting ice. Ahead of the front, the habitat is unsuitable for the species (the ice); behind the front, the habitat is suitable (the open water). The engineering action of the population moves the boundary ahead (the melting). This modelling approach leads to a time-dependent free boundary problem where the boundary corresponds to the edge of the population front.

In this talk, we present a novel model for the spread of ecosystem engineers as a free boundary problem. We derive the semilinear parabolic equation from an individual random walk model. The Stefan condition for the moving boundary is replaced by a biologically derived two-sided condition that models the movement behaviour of individuals at the boundary as well as the process by which the population moves the boundary to expand their territory.

We then prove local and global existence and uniqueness of solutions to the equations. We use a variational approach, define a specific functional corresponding to our system, and then apply the theory of nonlinear evolution equation with a time-dependent subdifferential operator along with a fix point argument.

## Modelling the inflammatory response - spatial considerations in the resolution of inflammation

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There is growing interest in inflammation due to its involvement in myriad medical conditions. Recent investigations show that inflammation is actively controlled by anti-inflammatory processes that can be modulated therapeutically. Accordingly, the mechanisms that resolve inflammation are of great interest, the interactions between macrophages and neutrophil-mediated pro-inflammatory processes in particular.

Existing mathematical models describing macrophage-neutrophil interactions are limited by their design, which generally takes the approach of spatially averaging biological quantities across the affected tissue. Assuming spatial homogeneity becomes increasingly spurious as the spatial scale of the damage increases, with clusters of neutrophils causing significant local tissue damage, while inflammation may resolve elsewhere. Furthermore, recent evidence points to aspects of the inflammatory response being modified under ageing and trauma, with changes in e.g. directed neutrophil motility and the macrophage functional response potentially influencing long-term outcomes.

We deploy a series of models that describe the interactions between populations of macrophages, active and apoptotic neutrophils and groups of chemicals that act as pro- and anti-inflammatory mediators, focusing throughout upon spatially-dependent facets of the inflammatory response. Via a hybrid approach, in which we combine a PDE-based description of mediators with an individual-based cellular automata description of the cell populations, we examine how variation in key model parameters can affect the spatial homogeneity of the outcome. In particular, we address the questions of whether initially localised damage can invade neighbouring healthy tissue, and the extent to which sub-optimal directed cell motility (such as that associated with ageing, or inflammatory conditions such as chronic obstructive pulmonary disease) can impact upon the long-term outcome. We illustrate that changes to the values of physiologically-relevant parameters can act as a switch between healthy and pathological scenarios; with careful parameterisation, our approach exhibits scope for elucidating how these key mechanisms could be actively manipulated to potentially identify new therapeutic interventions.

## Modeling of “replicator - genetic parasites” dynamics and coexistence

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Genetic parasites are ubiquitous satellites of cellular life forms. Theoretical considerations and computer simulations suggest that emergence of genetic parasites is intrinsic to evolving replicator systems (Koonin et.al, Biol Direct 2017). Here we study a series of non-linear models of replicator-parasite coevolution. Using methods of bifurcation analysis, we analytically determine the conditions for stable coevolution of genetic parasites and their hosts coevolution and reveal parametric domains of different patterns of the model behaviors, in particular, we describe some criteria of approaching “dangerous boundaries”. We show that in logistic-like Volterra type models the evolutionary dynamics of a parasite that initially evolves from the host through the loss of the ability to replicate autonomously must substantially differ from that of the host, for a stable host-parasite coevolution regime to be established. More specifically, stable coevolution becomes possible in models where only the reproduction of the host but not that of the parasite depends on the carrying capacity of the environment (Berezovskaya et.al., Biol Direct 2018). It is important that this model shows that replicator – genetic parasite coexistence is possible but not inevitable. Next, we construct the model assuming the ratio-dependence of host- parasite interactions and parasite fertility. Such type of interactions was proposed and justified in (Arditi, Ginzburg, Theor. Biol. ,1989); the main properties of the ratio-dependent predator-prey models were studied in (Berezovskaya, Karev, Arditi, Math. Biol., 2001). We construct a phase-parametric portrait of the model and trace a sequence of dynamic behaviors of the system under variation of the model parameters; in particular, we show that the replicators and genetic parasites can coexist in stable regimes in large domains of parameters and initial conditions.

# The transfer of honey bee disease in heterogeneous landscapes

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The transference of disease between honey bee colonies is poorly understood. In the following talk, we present a framework for modeling the incidence of disease between honey bee colonies in a heterogeneous landscape. We measure the effects of worker confusion, pesticide use, and drone movement on the spread of disease for different configurations of commercial honey bee colonies. Our model presents most likely scenarios for how diseases may spread between colonies and can help inform mitigation strategies.

## A Matrix Form of the General Laplace Kernel

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Integrodifference equations (IDEs) are often used for discrete-time continuous-space models in mathematical biology. The model includes two stages: the reproduction stage, and the dispersal stage. The output of the model is the population density of a species for the next generation across the landscape, given the current population density. Most previous models for dispersal in a heterogeneous landscape approximate the landscape by a set of homogeneous patches, and allow for different demographic and dispersal rates within each patch. Some work has been done designing and analyzing models which also include a patch preference at the boundaries, which is commonly referred to as the degree of bias. Individuals dispersing across a patchy landscape can detect the changes in habitat at a neighborhood of a patch boundary, and as a result, they might change the direction of their movement if they are approaching a bad patch.

In our work, we derive a generalization of the classic Laplace kernel, which includes different dispersal rates in each patch as well as different degrees of bias at the patch boundaries. The simple Laplace kernel and the truncated Laplace kernel most often used in classical work appear as special cases of this general kernel. The form of this general kernel is the sum of two different terms: the classic truncated Laplace kernel within each patch, and a correction accounting for the bias at patch boundaries.

## Modelling calcium signalling in cancer growth

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Calcium ( $\text{Ca}^{2+}$ ) is a life and death signal, the most crucial second messenger in the body, carrying important information across all our cells. In particular,  $\text{Ca}^{2+}$  has been shown to play a crucial role in cancer invasion and metastasis by orchestrating cell proliferation, adhesion, migration and apoptosis. Mechanisms behind cancer often involve changes at the molecular level, which for the  $\text{Ca}^{2+}$  signalling toolkit have been linked to alterations in  $\text{Ca}^{2+}$  pumps and  $\text{Ca}^{2+}$  conducting channels such as the inositol-1,4,5 trisphosphate ( $IP_3$ ) receptor. In this talk we review these changes and present one of the first mathematical models of calcium signalling in cancer. The model builds on well-established minimal calcium models coupled with recent cancer models and consists of coupled nonlinear differential equations for the density of cancer cells, the cytosolic  $\text{Ca}^{2+}$  concentration and the dynamics of the  $IP_3$  receptors. We study the model analytically and numerically and explore the role of  $\text{Ca}^{2+}$  signalling in various cancer types. Our work provides new insights into the significant role of  $\text{Ca}^{2+}$  in cancer progression and sets the stage for developing the novel area of  $\text{Ca}^{2+}$  transport in oncology research.

## Seasonal Variation in a Predator-Predator-Prey Model

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Predation behaviour of some predators changes according to seasonal variation in prey availability. As a result, the empirically observed functional response can change from saturating to sigmoidal, corresponding to specialist and generalist predation, respectively. Recent work analyzed a two-season predator-prey model of the great horned owl (*Bubo virginianus*) and the snowshoe hare (*Lepus americanus*), where this shift from generalist to specialist has been documented empirically. We expand that model to include the Canadian lynx (*Lynx canadensis*), which is a specialist predator in both seasons and the most important predator on the snowshoe hare. We study the qualitative behavior of this predator-predator-prey model. In particular we find conditions for coexistence of the two predators on a single prey. We use invasion analysis to determine conditions for coexistence. We use averaging techniques and numerical simulations to study the effect of seasonal variation on the coexistence conditions.

## Dynamics of the Selkov oscillator

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The Selkov oscillator is a simple mathematical model, a system of two ordinary differential equations, describing the metabolic pathway of glycolysis. Glycolysis is a central part of the energy metabolism that almost all living organisms have in common. Selkov's model was one of the first to mathematically describe the autonomous oscillations observed in experiments under constant substrate supply. To complete the analysis of the system and be able to identify all possible phase portraits, we studied the long term behavior of the solutions via a Poincaré compactification. The model obeys the expectations on a biological oscillator insofar as if there exists a periodic solution it is stable. In addition if the unique steady state is stable all bounded solutions eventually converge to it. At the same time it is the case that irrespective of the choice of parameters there are always solutions tending to a point at infinity. Furthermore it turns out that if the phase portrait does not correspond to one of those above then all solutions except the steady state either tend to a point at infinity or oscillate in a way that every variable takes on arbitrarily large and small values. It is not clear yet whether there really exist parameters resulting in this latter dynamics whereas the occurrence of the first two phase portraits is guaranteed for an appropriate parameter choice.

## LINEAR TRANSIT COMPARTMENT PHARMACOKINETIC MODELS AND EQUI-DOSING REGIMEN REGIONS

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Mathematical models for absorption, distribution and elimination of drugs are common in the pharmacokinetics (PK) literature. A drug's route through the body to its pharmacological effect site is modelled as a number of compartments, with transfer between compartments governed by pharmacokinetic rate laws. It is common to consider only one or two compartments, with linear pharmacokinetics. However, such models are not sufficient to capture delay-type effects, whereby some time passes before the drug appears at measurable levels in the systemic circulation. Lag-time models are sometimes used to model delay, but consideration of multiple transit compartments to effect delay is appealing due to a more mechanistic nature and mathematical tractability.

Here, we extend an existing transit compartment model analysis to present new analytical solutions for important multi-bolus dosing scenarios. Further, we introduce the idea of equi-dosing regimen regions for PK models, to summarise the regions of dosing parameter space corresponding to safe and effective dosing.

## The Mathematical Role of Immunity on the Within-Host Malaria Parasite Dynamics

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Within-host malaria parasite dynamics involve the interaction of different population groups. These are the healthy red blood cells (HRBC) and different parasite forms such as liver stage parasites, free-floating merozoites, parasitized red blood cells (PRBC), and the sexual parasite forms-gametocytes, the forms transmissible to mosquitoes. Additionally, the human's innate immune cells and adaptive immune cells work to counteract/inhibit the parasites effects within the human. In my talk, I will explore the mathematical dynamics of these interacting populations and the corresponding disease related implications such as disease severity within an individual.

## Modeling microbial community dynamics using genome scale metabolic models.

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With the advent of high throughput genetic sequencing technology and the resulting genome wide reconstruction of metabolic pathways, computational methods have been developed to analyze and draw insight from such large scale models. To enable computation of relevant model outcomes, constraint based reconstruction and analysis (COBRA) investigates steady state metabolism with a focus on metabolic reaction fluxes. Perhaps the most basic COBRA method, called *flux balance analysis* (FBA) computes reaction fluxes under the assumption that the cell will optimize for growth over the set of internally balanced fluxes, which correspond to the kernal of a stoichiometric matrix, constrained to some maximum fluxes. Flux balance analysis therefore provides a rate of increase of biomass which can be interpreted as a growth rate for a cell, and a subset of the computed fluxes provide an exchange rate of metabolites with the environment. By interpreting constraints on nutrient exchange reactions within individual metabolic networks of community members as functions of the shared environmental metabolite pool, the coupled system of microbial community & environment can be modeled. We call such a model a *dynamic community FBA model*.

We analyze the general properties of a dynamic community FBA model of species in a chemostat reactor. Such a model is similar to an ordinary differential equation, with the notable complication that computation of the vector field requires solving a linear program at each point to optimize reaction fluxes within each microbe. We show using a community of simplified microbial metabolisms that community metabolic modeling has the capacity to capture higher order dynamics within a community, a feature missing from traditional Lotka-Volterra community models. We also analyze the chemostatic equilibrium states of the model, which reflect possible stable communities of microbes. From these, a further optimization problem allows us to predict microbial relative abundances from the set of metabolisms, provided metabolite uptake parameters are known. We also show that the model can be approximated with a system of ODEs built using an energy-like function which enforces the optimization.

# Geometrical analysis of mixed-mode bursting oscillations in a multiple-timescale model of bursting electrical activity

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The phantom bursting model was introduced to describe the episodic bursting of the pancreatic  $\beta$ -cells, where active phases are interspersed by silent ones. The model is characterised by two slow and two fast variables with the two slow variables having very different time scales [1]. Considering the different time scales of the four variables of ordinary differential equations, Mixed-Mode Bursting Oscillations (MMBOs) solutions can be found. MMBOs are characterized by both small-amplitude oscillations (SAOs) and bursts consisting of one or multiple large- amplitude oscillations (LAOs) [2].

Here we focus our attention on the mechanism that generate the MMBOs due to both canards and delayed-Hopf-bifurcation [3]. Canards are central to the dynamics of MMBOs and we study them starting from the folded singularities, that are equilibria of the desingularized system of the phantom burster model. The canard phenomenon explains the very fast transition upon variation of a parameter from a small amplitude limit cycle via canard cycles to a large amplitude relaxation cycle. Furthermore the presence of the subcritical Hopf bifurcation via fast/slow analysis of the fast subsystem is found. A detailed geometric explanation of MMBOs is done.

## References

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- [3] Richard Bertram, Joseph Rhoads, Wendy P. Cimbara, *A Phantom Bursting Mechanism for Episodic Bursting*, Bull. Math. Biol. 70(1979) (2008) 1989-2017.

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## Spectral early warning signals improve tipping point detection and description

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Theory and observation indicate that many complex systems exhibit tipping points - thresholds involving an abrupt and irreversible shift to a contrasting dynamical regime. These shifts are commonly referred to as critical transitions. Early warning signals (EWS) for critical transitions could allow early intervention to prevent unwanted transitions such as ecosystem collapse. Standard EWS seek trends in simple statistical metrics such as an increase in variance and autocorrelation. However, they provide similar trends preceding smooth transitions, such as the onset of cycles that occurs at a Hopf bifurcation, and can fail to signal critical transitions under certain regimes of environmental noise. Here, we show from mathematical principles and simulation, that information available in the power spectrum improves our ability to detect and describe an upcoming transition. Specifically, the peak of the power spectrum captures changes in bifurcation proximity, and the shape of the power spectrum - quantified using AIC weights - provides information on the bifurcation type. We validate this approach against predator-prey chemostat data, showing that these spectral EWS predict and, unlike standard EWS, characterise the bifurcations. We conclude that EWS can benefit from evaluating the full information available in the power spectrum in conjunction with standard EWS like variance and autocorrelation.

# Spatio-temporal heterogeneities in a mechano-chemical model of collective cell migration

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Small GTPases, such as Rac and Rho, are well known central regulators of cell morphology and motility, whose dynamics also play a role in coordinating collective cell migration. Experiments have shown GTPase dynamics to be affected by both chemical and mechanical cues, but also to be spatially and temporally heterogeneous. This heterogeneity is found both within a single cell, and between cells in a tissue. For example, sometimes the leader and follower cells display an inverted GTPase configuration. While progress on understanding GTPase dynamics in single cells has been made, a major remaining challenge is to understand the role of GTPase heterogeneity in collective cell migration.

Motivated by recent one-dimensional experiments (e.g. micro-channels) we introduce a one-dimensional modelling framework allowing us to integrate cell biomechanics, changes in cell size, and detailed intra-cellular signalling circuits (reaction-diffusion equations). Using this framework, we build cell migration models of both loose (mesenchymal) and cohering (epithelial) tissues. We use numerical simulations, and analysis tools, such as local perturbation analysis, to provide insights into the regulatory mechanisms coordinating collective cell migration. We show how feedback from mechanical tension to GTPase activation lead to a variety of dynamics, resembling both normal and pathological behaviour.

**Subdiscipline** Developmental Biology.

# Life is not a long quiet river: modelling population genetic divergence when migration is fluctuating

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A fundamental aspect of evolutionary theory is our understanding of population genetic divergence, whereby populations connected by gene flow may diverge at neutral loci and for adaptive traits. This forms the basis for inferring population connectivity from genetic data, predicting local adaptation in the face of gene-flow, or the development of incompatibilities between incipient species. While evolutionary theory has typically envisioned gene-flow as a steady, continuous connection among populations, it is increasingly clear that several processes (climatic events, anthropogenic transport, group dispersal) can make gene-flow fluctuating and intermittent, rather than steady and continuous. There is however little theory on how fluctuating migration impacts divergence compared to smooth migration. Some results suggest that variable migration should decrease effective migration rate, but they assumed uncorrelated fluctuations and neutral variation only. Here we analyze mathematically a stochastic model to describe in continuous time the genetic divergence of connected populations, where migration can be pulsed (intermittent). Our model covers a range of migration scenarios (unidirectional, synchronous or asynchronous) and genetic scenarios (neutral markers, locally adapted mutations, incompatible mutations). In a slow-fast limit, we derive simple analytical approximations regarding whether pulsed migration affects population divergence (probability of identity) compared to a steady flow of similar intensity, and validate them with stochastic simulations. We find that migration pulsedness can not only increase, but also decrease, the rate of population divergence. We summarize how predictions depend on the mode of migration and on the type of genetic variation, and provide graphical interpretations in terms of probabilities of fixation. We finally discuss how pulsed migration might leave a footprint in genomic data.

## A mathematical model of osteochondral defect regeneration

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Osteochondral defects are defects of cartilage and underlying subchondral bone, typically occurring in weight bearing joints such as the ankle and the knee. Osteochondral defects are both a leading cause and result of osteoarthritis, the most common type of arthritis in the UK. Defects can occur through acute trauma, natural wear and tear of the joint, and underlying disease of the bone. Defects often begin as small lesions of cartilage, which when left untreated become full-thickness defects, leaving underlying subchondral bone exposed. Though osteochondral defects can spontaneously repair, the tissue is usually fibrous, typically leading to subsequent degradation of the newly regenerated tissue.

The mechanism behind osteochondral defect repair is elusive, with no golden standard surgical treatment currently available. We present a mathematical model of osteochondral defect regeneration to uncover the underlying mechanisms of healing. Lydon et al<sup>1</sup> recently showed osteochondral defects in ovine models heal via endochondral ossification; the process of bone formation in the presence of cartilage. Their findings show healing begins with cartilage formation first occurring along the edges of the defect, filling from the sides inwards and upwards until the defect fills. Once this process has occurred, endochondral ossification takes place, replacing cartilage with bone, with a layer of cartilage left remaining at the top of the defect.

Our mathematical model successfully encapsulates the endochondral ossification process by showing cartilage formation followed by matrix calcification and ossification. The driving mechanisms of healing in our mathematical model are modelled by cell migration, proliferation and hypertrophy, matrix formation and conversion, and nutrient and growth factor diffusion, both spatially and temporally. The stages of healing are regulated by growth factors, highlighting their important role in the successful healing of an osteochondral defect.

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## Functional specialization under multiple tradeoffs mediated by resources

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A tradeoff is a functional relationship between two traits. Tradeoffs are considered to play a central role in shaping the patterns of biodiversity in ecological communities. In spite of this prominent role, their characterization and consequences are still hard to assess mainly because of the interplay among multiple tradeoffs. From classical ecological models handling single tradeoffs, it is known that specialization is expected when the tradeoff is characterized by convex relationships, whereas no specialization is expected when the tradeoff follows concave curves. An elementary question is the understanding of how the existence of multiple tradeoffs corroborates or alters the scenarios presented by those classical models. In order to tackle this problem, here we study a resource-based model that encompasses multiple tradeoffs that are mediated by the acquisition and the processing of resources to assess the levels of functional specialization under several scenarios. Here we are concerned with two tradeoff types that are related to the metabolic properties of organisms: the tradeoff between resource uptake rates, and the rate-yield tradeoff. The problem is first addressed for the case of two resources and then generalized for an arbitrary number of resources. By means of extensive computer simulations, we show that very complex ecological patterns emerge under multiple tradeoffs. The outcomes can be quite distinct from those expected under the light of the results of classical ecological models.

## Mechanistic Immuno-Viral Dynamics Modeling Platform for HIV Cure Drug Development

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Current antiretroviral therapy (ART) effectively controls HIV in most patients, but does not cure it. Side effects from life-long ART and risks of viral mutations become long-term burdens for HIV patients. To address the limitations of ART and develop new therapy towards a HIV cure, novel approaches – such as reactivation of latent provirus (“flush”), killing of infected cells, and immunotherapies – are being explored. However, it is an open question whether these approaches – either alone or together – might lead to a cure. Mechanistic mathematical models that describe both within-host viral load dynamics and immunologic control of HIV infection are essential to integrate clinical data, assess therapeutic response, and generate hypotheses in support of HIV cure drug development. We therefore built the Latent Viral Dynamics Model (LVDM) platform, a mathematical model based on [1] and [2] that integrates mechanisms that may lead to a cure. We fit the LVDM to an integrated heterogeneous dataset ( $N=896$ ) consisted of viral load (VL) data during the analytical treatment interruption (ATI) phase provided by the AIDS Clinical Trials Group (ACTG), and data during the ART treatment phase from an internal Phase 3 clinical trial. Both population estimates and inter-subject variabilities of 6 selected parameters are reliably estimated. Fitting results show that the LVDM can accurately capture the viral dynamics during both ART and post-ATI. Estimated parameters are all within biologically plausible ranges. We further created virtual populations from the estimated LVDM parameters, and predicted outcomes of HIV cure trials using large scale clinical trial simulations (CTS) with different treatment schedules. Simulations based on parameters of individual patients showed strong correlation between the potency of HIV-specific immune killing effects (from CD8<sup>+</sup> T cells and other effector cells) and the post-ATI VL set-point ( $R^2 = 0.67$ ,  $p = 3.0 \times 10^{-19}$ ), which suggested the possibility of achieving low post-ATI viral set-point by boosting up HIV-specific immune responses. These results quantitatively inform the degree of immune response required to achieve long-term HIV post-treatment control or cure. The LVDM stands as a candidate model to predict viral and immunological responses to potential curative interventions. The LVDM platform will be continuously developed and will provide critical support for identifying new targets, generating hypotheses about combination therapies, and designing HIV cure trials.

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# Qualitative behavior of AIDS in a homosexual population

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## Abstract

The main idea of this work is to build a mathematical model that provides a better understanding of the qualitative behavior of AIDS in a male homosexual population. This model initially assumes a homogeneous combination taking three possibilities of clinical cases: Seropositive, full AIDS and the associated complex relationship (ARC). The proposed mathematical model is described by a dynamic system of nine differential equations which involves nine unknown functions.

**Keywords:** ARC, propagation of AIDS, mathematical Epidemiology, qualitative behavior.

## Network inference of the circadian clock

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The mammalian circadian rhythm is governed by the master clock located in the suprachiasmatic nucleus (SCN). The master clock is composed of thousands of cells. The network structure among cells play an important role in the SCN function: synchronization, entrainment to light, etc. Previous studies used the oscillating time course data of explanted mice SCNs during the resynchronization after the desynchronization with neurotoxin. This is because the normal network has very strong coupling resulting in many false positives. However, resynchronization experiment takes a long time and the recovered structure may not be similar to the normal network. We develop our own method, which can infer the network structure with strong couplings. With this method, we analyzed time series data of 2,500 cells from mice SCNs. It takes shorter time and one can obtain the normal structure of the SCN without weakening of the network. Our method can infer the directionality of the coupling, which was not able with previous studies.

## How to incorporate genetic information into models for pesticide degradation in soils

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Traditional biogeochemical models include state variables such as microbial biomass pools that in practice cannot be measured. Modern molecular biology tools can provide quantitative information on functional microbial groups involved in a range of biogeochemical processes. This data can be used to develop models that accurately capture microbial population dynamics and metabolism of microbial driven matter cycling processes. We developed such a model to simulate pesticide degradation in soils. This mechanistic model is formulated as a set of ordinary differential equations. We assume that the pesticide MCPA is the sole source of carbon and energy for bacterial growth. The model includes an expressed gene pool representing the gene encoding for the enzyme tfdA, which is known to be involved in the rate-limiting step of MCPA biodegradation. We describe the activation of these genes by MCPA using a Hill function. The microbial degrader population is divided into three subpopulations: viable cells that metabolize MCPA; viable cells that do not; and dead cells. The consumption of MCPA drives microbial growth and maintenance; a fraction of the carbon in the consumed pesticide is reduced and released as  $CO_2$ . The model was calibrated against data on mineralized  $^{14}C$ -MCPA as well as tfdA mRNA and DNA abundance (Bælum et. al, 2008). We compare this genetically-informed model with simpler biomass-based compartmental biogeochemical models to assess the value of genetic observations in this context.

Bælum, J., Nicolaisen, M.H., Holben, W.E., Strobel, B.W., Sørensen, J., Jacobsen, C.S., 2008. Direct analysis of tfdA gene expression by indigenous bacteria in phenoxy acid amended agricultural soil. ISME Journal 2, 677.

## Evolution of dispersal toward fitness for predators with predation-induced dispersal

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In many cases, one may observe that dispersal of living organism is affected by circumstance of the environment they reside. In particular, we will consider predator's dispersal, called a predation-induced dispersal (PID), which represents the change of predator's motility depending on the difference between the maximal predation rate and the death rate of predators in a region. In this presentation, we examine predator-prey models with ratio-dependent functional responses under no-flux boundary conditions where the predators have the movement following the rule of PID to understand how PID affects the fitness of species in a heterogeneous region. To achieve our goal, we first study the local stability of prey, when the predators are absent, for model with PID and linear dispersal, respectively. Then the local/global bifurcation from semi-trivial solution is investigated for models with two different dispersals. Finally we compare the results for the model with PID with one of model with linear dispersal. We conclude that a nonuniform dispersal of predator responding to their given heterogeneous environment, increases the predator's fitness and so the predator with PID can invade with more chance in a region when rare, even the case where the predator with linear dispersal also can make invasion in a certain region. The results are obtained by an eigenvalue analysis of the semi-trivial solutions for the linearized operator derived from the models with PID and linear dispersal, respectively. Finally ecological interpretation based on the results obtained will be given with the simulations.

## Evolutionary Dynamics in a Group Population Structure with Barriers to Entry

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The evolution of cooperation has been studied in many systems, from bacterial communities to human populations. It is well known that population structure is crucial to a system's dynamics. In human populations, group memberships are critical. Humans often meet and interact with each other due to common group memberships. There exist network-based models to study human dynamics, but they generally do not allow for multiple group affiliations or incorporate barriers to group entry. In this work, we present a framework in which individuals in a group-structured population interact, through an evolutionary game, with those who share their groups. Individuals update stochastically, with strategy and group memberships subject to evolutionary updating. We impose realistic barriers to group entry based on group size. We find that with barriers, cooperation can emerge, but that it is most favored when we allow for the existence of "loners": a changing subset of individuals who spend a temporary "time-out" period not interacting with others. This work provides an analytical framework in which behavior in realistic population structures can be studied, and adds to a growing body of literature that recognizes the existence of loners as vital parts of systems.

## HOPF BIFURCATION IN A THREE-SPECIES INTRAGUILD PREDATION MODEL WITH STAGE STRUCTURE

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We consider the tri-trophic community module consisting of a predator and its prey that share a common resource. This combination of predation and competition is called *intraguild predation* (IGP), and is known to be common and widespread in nature and ecological systems. The IG predator depends solely on both the IG prey and the basal resource for its sustenance. We also refer to the IG predator as an *omnivore* since it feeds on more than one trophic level. Early theoretical works on IGP models (see e.g. Holt and Polis, 1997) suggest that a general criterion for coexistence for IGP systems requires the IG prey to be superior than the IG predator in competing for the shared resource, while the IG predator must gain significantly from its consumption of the IG prey.

In this talk, we consider a three-species IGP model where in the IG prey population is partitioned into juvenile and adult stages. In our model, we assume that the juvenile IG prey have little ability for predation and are able to avoid the IG predators by taking refuge. Moreover, the maturation age of the IG prey population is reflected by a time delay. Varying this delay parameter may cause switches in the stability of the coexistence equilibrium. These stability switches occur at a critical delay values where Hopf bifurcation occurs. We study the criticality of these Hopf bifurcations using the theory of normal forms and center manifold reduction. This allows us to determine the stability of the branch of periodic orbits that bifurcates. These additional insights give us a better understanding of the dynamics of the IGP model, particularly the effects of introducing stage structure in the coexistence of species.

# THE REPLICATOR DYNAMICS FOR MULTILEVEL SELECTION IN EVOLUTIONARY GAMES

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In this talk, we consider a stochastic model for evolution of group-structured populations in which interactions between group members correspond to the Prisoner's Dilemma. Selection operates at two organization levels: individuals compete with peer group members based on individual payoff, while groups also compete with other groups based on average payoff of group members. This creates a tension between the two levels of selection, as defectors are favored at the individual level, whereas groups with at least some cooperators outperform groups of defectors at the between-group level. In the limit of infinite group size and infinite number of groups, we derive a non-local PDE that describes the probability distribution of group compositions in the population. For special families of payoff matrices, we characterize the long-time behavior of solutions of our equation, finding a threshold intensity of between-group selection required to sustain density steady-states and the survival of cooperation. When all-cooperator groups are most fit, the average and most abundant group compositions at steady-state range from featuring all-defector groups when individual-level selection dominates to featuring all-cooperator groups when group-level selection dominates. When the most fit groups have a mix of cooperators and defectors, then the average and most abundant group compositions always feature a smaller fraction of cooperators than required for the optimal mix, even in the limit where group-level selection is infinitely stronger than individual-level selection. In such cases, the conflict between the two levels of selection cannot be decoupled, and cooperation cannot be sustained at all in the case where between-group competition favors an even mix of cooperators and defectors.

- Subdiscipline: Population Dynamics, Ecology and Evolution
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## Compartmental Modeling of Calcium Dynamics in Astrocytes

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Several contemporary studies show that astrocytes, a type of glial cell, are fundamental to a variety neural functions ranging from metabolic support to higher cognition such as recollection memory. This has led to the introduction of astrocytic dynamics into neural modeling. Most cellular functions in astrocytes are triggered by an increase or decrease in calcium concentration within the cytosol. Previous work treated astrocytic dynamics by representing calcium concentration as a point source or a completely spatial model in the cell. We now know that the role of the astrocyte takes many different perspectives. This work, which is inspired by *in vivo* recordings of astrocytes in the ferret visual cortex, models the different levels of intracellular calcium activity in the astrocyte. In the model, we create a framework to enable the exploration of spatial calcium dynamics in astrocytes. We consider five astrocyte processes, modelled as five spatially partitioned compartments representing branches. Over each compartment we solve a system of differential equations for intracellular calcium dynamics. A branching structure, while not as general as a full 2D or 3D spatial simulation allows the study of astrocytes cellular properties over extended regions of space. Studying a spatial representation of the processes will help investigate the role of astrocyte morphology and spatially varying physiology in calcium signal propagation as well as developing intuition on the functional relationship between different levels of activity in the cell.

## A Stochastic Model of Filament Transport by Motor Proteins

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Intermediate filaments are a key component of the cytoskeleton. Their transport along microtubules plays an essential role in the control of the shape and structural organization of cells. In order to understand how a cell regulates this transport we present a model of elastic filament transport by microtubule-associated dynein and kinesin. In the model we investigate how filament length, elasticity, and motor capacity affects the system. By comparing simulations where the two motors have exponential off-rates, catch bond off-rates and combinations of the two we investigate the effects of motor properties on filament transport. In our simulations, when the off-rates of the two motors are different the catch bond motor dominates. Filament elasticity modulates the coordination of motors along the length of the filament and thus alters the speed of transport.

## Comparing Efficacy of Hydroxyurea and IFN- $\alpha$ Treatment in MPN Patients

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The chronic Philadelphia-negative myeloproliferative neoplasms (MPNs) are neoplasms acquired on the stem cell level. Patients with MPNs can survive for decades as the diseases have a low incidence and slow progression. The diseases are tightly linked to the JAK2V617F mutation which is observed in many patients. The JAK2V617F mutation burden is a notable marker of disease severity.

Through a close collaboration with medical doctors at the Department of Haematology, Zealand University Hospital, Roskilde, Denmark access to data from the DALIAH trial (#EudraCT 2011-001919-31) is available. The DALIAH trial is an ongoing randomized open-label phase III clinical trial focused on comparing the efficacy of hydroxyurea (HU) and low-dose interferon- $\alpha$ -2 (IFN) treatment. Data from the DALIAH trial includes serial measurements of the JAK2V617F allele burden throughout treatment as well as leucocyte and thrombocyte count.

This unique collaboration leads to both data-driven and model based analysis of the DALIAH trial results backed by and challenging medical and clinical intuition.

HU is the standard treatment in MPNs but it is thought to not affect the disease at the stem cell level. IFN on the other hand has shown great promise in reducing the JAK2V617F allele burden at stem cell level. Through mechanism based modelling it is possible to distinguish where the different treatments affect the disease by using the data from the DALIAH trial.

Preliminary results indicate that HU treatment in some patients decrease the JAK2V617F allele burden on the short term until patients develop a resistance, while IFN treatment (in responders) leads to exponential decay in the JAK2V617F allele burden, though for some patients the effect of IFN treatment is only noticeable after 1-2 years of treatment.

## Cellular dialogues that enable self-organization of dynamic spatial patterns

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Traditionally, biological pattern formation has been explained through reaction-diffusion models that describe how interacting chemicals can self-organise into stripes, spots and waves. Despite increased experimental evidence that these models can accurately describe specific developmental processes, such models rely on partial differential equations and instability mechanisms which do not take into account individual cells. We developed a cellular-automaton-based framework for understanding multicellular pattern formation that explicitly incorporates individual cells and how they respond to signalling molecules they sense and produce. Our framework is based on a hybrid model of a cellular automaton for describing gene-expression levels and responses of individual cells and reaction-diffusion equations for describing the diffusing signalling molecules. With rules for how the chemicals interact, we observed that our system was able to generate a variety of complex self-organized dynamic patterns such as oscillations, travelling waves, and patterns that evolve in a chaos-like manner. Through an exhaustive computational search and employing analysis algorithms that we developed, we identified the gene networks and conditions under which these patterns can form. This allowed us to classify all gene networks with two signalling molecules depending on their dynamic behaviour. We then formulated an analytical theory that accurately predicts the gene circuits and parameters required for dynamic pattern formation. Finally, we expanded our work to explore cell-cell communication in more complex settings. Our work provides a comprehensive overview of dynamic pattern formation in small populations of communicating cells. Understanding how self-organized patterns arise in multicellular systems has implications for engineering mammalian tissues and organs.

## Noise Assisted Extinction of Chaotic Cancer Model

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**ABSTRACT:** Cancer is caused by abnormal growth regulation of normal cell. In this talk, a 3D deterministic mathematical model is proposed, governing by healthy tissue cell (host cell), immune-effector cell and tumor cell. The stability of biological meaningful equilibria and the existence of Hopf-bifurcation have been discussed. The periodic solution of the system directs to chaotic phenomena which has been verified by the 0-1 test. In addition, persistence and global solution have been analyzed by introducing additive environmental noise in the proposed system to ensure the positivity and boundedness of the deterministic system. Tumor extinction scenario is captured from the stochastic environment in periodic co-existence domain of the deterministic system.

## Metrics for Regulated Biological Systems

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The assessment of graphs through numerical metrics has long been a hallmark of biological network analysis. However, typical graph metrics ignore regulatory signals that are crucially important for optimal system design and analysis, for instance, in metabolic, physiological, or ecological systems. Here we introduce adjusted metrics, such as *efficiency*, *reachability*, and *clustering coefficient*, that are applicable to both static networks and dynamic systems. These metrics are the result of expanding a regulated system into a bipartite graph with metabolite or species nodes linked through enzyme, reaction, or interaction nodes. Regulation is incorporated through signals from an original node to the appropriate enzyme/reaction/interaction nodes. Once these signals are included, the system can be reduced back to a regular graph, for which the new metrics are calculated. The effects of regulation on a system can thus be quantified by comparing the various metrics of the regulated system with the corresponding metrics of the non-regulated system. The new metrics may serve as a guide for identifying potential drug targets, as tools to enhance microbial production in metabolic engineering, and as a way to identify species or metabolites that are particularly well suited for model reduction toward lower-dimensional systems.

## **Individual vaccination choice and optimal budget allocation for vaccination campaign**

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**Presenter : Aniruddha Deka**

### **Subdiscipline Area**

- Mathematical Epidemiology
- Population Dynamics, Ecology and Evolution

## **Abstract**

The paper aims to investigate optimal budget allocation for vaccination campaign when vaccination is voluntary for an infectious disease like seasonal flu. We use evolutionary game theory and compartmental model of disease transmission to analyze how individual vaccination choice influence the budget allocations and vice versa. We also use optimal control theory to determine

- The budget allocated that minimize the cost of disease control.
- The budget allocated that minimize the time of disease control

Under voluntary vaccination campaign, high vaccine coverage cannot be taken for granted, as individuals free-riding behaviour plays a significant role in achieving the herd immunity level coverage. Our findings are useful to public health policymakers and may help to quantify certain parameters in budget allocations to control vaccine-preventable flu like diseases. The paper also illustrates that if optimal control is too early in the duration of outbreak, then cost of public health effort is higher. On the other hand, if it is too late, then infection prevalence rises, and so cost from infection will be high. So the problem reduced to find out an optimal starting and end time so that total cost from the mitigation of disease outbreak is minimum.

## Modeling the Growth and Sustainable Control of Invasive Eurasian Watermilfoil

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Eurasian watermilfoil (EWM - *Myriophyllum Spicatum*) is an invasive aquatic plant which was first introduced into North America in the 1940s (originating from Europe, Asia, and North Africa). Like other invasive plants, EWM has the ability to grow and spread quickly, forming dense monocultures, due to its ability to outcompete many native aquatic plants.

We begin by expanding on previous theoretical models [1], [2] to describe the growth of EWM in a dense single stand, using an ODE approach. This model is used to predict the total biomass of a single patch of EWM over a single growing season. Our new extension takes into account the winter months, and so can monitor EWM growth over multiple seasons. The novelty in this approach is that it takes into account the amount of carbohydrates that are stored in the plant roots at the end of the growing season. These carbohydrates help drive the initial EWM regrowth in the following growing season.

Several management strategies have been adopted to control this invasive species including mechanical harvesting, chemical use, use of bottom covers, and the introduction of a bio-control, the Milfoil Weevil (*Euhrychiopsis Lecontei Dietz*). These methods alone are not sustainable since they are expensive and take a great deal of effort to implement. Here, we extend our model, and show how these control measures might be combined to construct a sustainable management strategy.

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[2] Miller et al., 2011, Biocontrol 56: 935–945.

## Oncolytic virus treatment of cancer

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With our developing ability to genetically engineer viruses, there is renewed interest in using cancer-killing (oncolytic) viruses to treat cancer. In determining which viruses can potentially be used to treat cancer, an important consideration is the virus' preference for cancer cells over non-cancerous cells. Here we use ordinary differential equation models and spatially extended partial differential equation models to determine the viral characteristics needed for a virus to both kill all cancer cells, but to leave the majority of non-cancerous cells uninfected.

# Zero-Inflated and Over-Dispersed Species Arthropods Count Data With Fast Estimation of GLLVM

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Ecology is a part of biology that studies the interaction and relationship between organisms and their environment. Hence, the abundance and the distribution of organisms and spatial patterns of biodiversity are of great interests for ecologists. In this paper, we illustrate the implementation of GLLVM assuming a Negative Binomial model since overdispersion occurs due to an excess frequency of zeroes on a real dataset. The aim is to give an understanding of how a correlated discrete response is modeled using GLLVM and understand the pattern through residual ordination Sampling of this study was carried out in the Gunungsewu Karst area in Indonesia. Data was collected in 3 show caves and three wild caves. The show cave studied are Gong, Tabuhan, and Semedi. The three caves are located in Pacitan Regency, East Java. The wild caves investigated were the Paesan Cave in Gunungkidul Regency, Kalisat cave in Wonogiri District, and Ponjen Cave in Pacitan District. The selection of caves is done purposively and is based on the similarity of the character of the aisle which is classified as a cave fossil with horizontal thrust. Then, we fitted a count regression model with slope and logging covariates to select the number of latent variables used in the GLLVM, both AIC and BIC criteria were used

## Spatially explicit models simulate rich forest-grassland mosaics

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Mosaic ecosystems, where multiple land-states coexist spatially as alternative stable states, display distinct clustering of land-states. While factors facilitating coexistence have been investigated through empirical studies and models, their influence on spatial structure is little explored. We construct a spatially explicit agent-based model for a forest-grassland mosaic to analyze the dynamics resulting in these characteristic patterns. Using empirical data for the mosaics of Southern Brazil, we simulate the system and generate landscape vignettes. We compare these vignettes to satellite images of the region to evaluate the model's performance. Additionally, we explore parameter space to observe how the rates of transition between land-states impact spatial structure.

Through the inclusion of local spatial interactions and fire-mediated tree recruitment, our model reproduces several features of real-world mosaic spatial structure, including the number of forest patches and forest cover level. Varying rates of random disturbance, forest mortality, and forest recruitment impact the forest cover and spatial structure of the landscape. For a given level of forest cover, shifting the value of any rate can alter the number of forest patches, as well as patch perimeter. If random disturbance and either mortality or recruitment are varied simultaneously, the change in number of forest patches is larger than when a single rate is adjusted, suggesting these ecosystems are particularly susceptible to perturbations from combined disturbances. The relatively narrow range of conditions under which mosaics persist in the model points to the potential fragility of these ecosystems. Given that a parsimonious model generates such rich dynamics and spatial patterns, spatially explicit agent-based models for mosaics should be further explored.

## The evolution of strategies within a network harvesting common-pool resources

Isaiah Farahbakhsh (Presenter)<sup>a</sup>, Dr. Chris Bauch<sup>b</sup>, and Dr. Madhur Anand<sup>c</sup>

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Common-pool resources (CPR) have been a highly discussed topic in many diverse fields such as economics, sociology, applied mathematics, and ecology. These finite resources such as forests and fisheries are available for public extraction and therefore very susceptible to overuse by profit-seeking individuals. However, in many cases, resources have been able to persist sustainably without the presence of a central governing body due to social norms. This talk will present a network simulation mathematical model which explores the complex dynamics of a static social network of agents harvesting a CPR. The harvesting strategies of the agents evolve depending on the state of the resource as well as social norms. From the results, the emergence of cooperation and resource sustainability will be discussed in relation to critical regions in the system and self-organized criticality. Furthermore, the direct comparison of two commonly used strategy-evolving mechanisms often assumed in game-theoretic CPR models will be explored within this framework.

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## A. AUTHORS

Presenter: Dr. Matthew Faria

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## B. TITLE AND ABSTRACT

### Determination of a kinetic model of nanoparticle-cell interaction

Nanoengineering has devoted significant effort to the design of “stealth” nanoparticles, which can avoid recognition by the immune system, as well as “targeted” nanoparticles, which preferentially interact with particular cell types. Unfortunately, quantitative assessment of nanoparticle performance remains challenging even *in vitro*; reasons for this include settling effects, variations in experimental protocol, and labeling strategy. These artifacts dominate naïve attempts to compare results across particles, cell lines, and experiments, limiting (or completely restricting) the reusability of most studies. Here, we present a mathematical framework which envisions cell-particle interaction as a kinetic reaction on a surface. This framework is used in conjunction with a newly generated dataset of nanoparticle-cell association data to determine which of 5 candidate kinetic models best explains the underlying data. The complete model presented can be used as an experiment-independent, quantitative metric of nanoparticle stealth and targeting performance. This rigorous, quantitative approach reveals opposite conclusions from naïve, qualitative interpretation of cell-particle interaction data. Finally, we will briefly present a companion website which can be used to apply this analysis to new data from experimentalists.

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## C. SUBDISCIPLINE AREA

Immunobiology and Infection

## Networks provided from neuronal activity

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Stimulating a region of the brain, the potential of that region can be recorded, which will produce a time series. This time series indicates biophysical behaviors of the region. Through the visibility algorithm [Lucas Lacasa, 2008] we can obtain graphs of time series, in our case, from neuronal activity induced by eight different mice. Thus, we have eight readings where the initial stimulus is varied. These readings vary between 100 to 300 mA, and from -300 to -100 mA; so we can classify the readings according to sign of the injected stream. In this work, we found that some properties of the graph are conserved (and some others that do not) through different time series, coming from the same experiment.

## Numerical Methods for the Microscopic Cardiac Electrophysiology Model

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Several mathematical models are available for the simulation of the cardiac electrical activity at various scales. For instance, the bidomain model represents the cardiac action potential at the organ level. For studying propagation between a strand of myocytes, the microscopic model is based on an explicit representation of individual cells, similar to what is done for modelling propagation in single or small groups of neurons. At the microscopic level, the cardiac tissue can be viewed as two separate domains: the intra-cellular and extra-cellular domains, respectively  $\Omega_i$  and  $\Omega_e$  separated by cellular membranes  $\Gamma$ . The microscopic model consists in a set of Poisson equations, one for each sub-domain  $\Omega_i$  and  $\Omega_e$ , coupled on interfaces  $\Gamma$  with nonlinear transmission conditions involving a system of ODEs. Few numerical methods have been proposed in the literature for the microscopic model. We focus on the numerical solution of the microscopic model. An operator splitting method is used at each time step to solve two separate problems, namely the nonlinear ODE models representing the ionic activity on  $\Gamma$  and coupled linear space propagation problems on  $\Omega_i$  and  $\Omega_e$ . To handle the non-standard transmission conditions coupling the solutions on  $\Omega_i$  and  $\Omega_e$ , we propose a non-overlapping domain decomposition (DD) method. Then, we address convergence issues of this DD method and present numerical results for the microscopic models.

## THE DYNAMICS OF STOICHIOMETRIC PLANT-POLLINATOR-HERBIVORE MODELS AND PARAMETER SENSITIVITY ANALYSIS.

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Plant-pollinator interactions play an important role in the maintenance of the balance of nature. All organisms living in the environment are composed of different ratios of chemical elements. By considering the balance of essential chemical elements in nature, we can formulate mathematical models to study their role in the dynamics of the system as well as nature. By assuming herbivore as a predator to the plant, we formulate and analyze stoichiometric-plant-pollinator and stoichiometric-plant-pollinator-herbivore models. Our model includes a four-dimensional system of ordinary differential equations to represent the plant, pollinator, herbivore populations, as well as the varying nutrient levels of the plant. We analyze the dynamics of the system such as non-negativeness and boundedness of solutions, as well as the existence and stability of boundary equilibria. We perform a bifurcation analysis of the model and also a parameter sensitivity analysis of the model using Latin hypercube sampling and partial rank correlation coefficient technique.

## Modeling blood flow and oxygenation in a retinal microvascular network

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Glaucoma is the second-leading cause of blindness worldwide, and has been associated with impairments in blood flow and oxygenation of the retina. Historically, it has been assumed that the blood flow changes have been caused by a reduction in oxygen demand, but recent evidence has suggested the relationship may be more complicated. Here, mathematical models will be presented that predict microvascular blood flow and oxygenation of the retina, which imply the possibility that dysfunction in the regulation of blood flow may actually be a *cause* of oxygenation impairment, rather than an effect. An updated model that takes into account the heterogeneous structure of the retinal microcirculation will also be presented, which predicts tissue and vessel oxygenation in a non-uniform vascular network geometry using a method based on Green's functions. Model results suggest a large spread in tissue oxygen levels across the retinal arteriolar microvascular network, and that changes in blood oxygen saturation and blood flow regulation can lead to regions of hypoxic tissue that would not be predicted using averaged measurements of tissue oxygen levels. This model framework will be used in the future to make spatial predictions of retinal microvascular oxygenation under varying conditions, in order to identify possible correlations between hypoxic tissue regions and regions where the visual field is impaired in glaucoma patients.

## Evolutionary Game Theory with Applications to Behavioral Epidemiology

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Evolutionary game theory has become a general approach to studying a wide range of biological and social problems. In particular, it has proved useful in understanding human strategic behavior in social dilemma situations where people can cooperate for the common good. Notably, the tragedy of the commons can also arise as a result of free-riding in the important context of public health problems, such as vaccine compliance and antibiotics overuse. Understanding them through the lens of evolutionary game theory is a new promising direction. In this talk, we will discuss a series of our recent work along this line.

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**Progression of Numerical Techniques for Model Construction and Analysis**

In this talk, I will discuss the numerical techniques introduced to students in an undergraduate Mathematical Biology course. I will present the progression of laboratory sessions and exercises and will address how each of these activities enhances students' understanding of model construction and analysis. In addition, I will introduce the framework that I have developed of assigning final projects in this course and numerical methods that are required for the projects.

# The coexistence of competing consumers on a single resource in a hybrid model

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The question of whether and how two competing consumers can coexist on a single limiting resource has a long tradition in ecological theory. We build on a recent seasonal (hybrid) model for one consumer and one resource, and we extend it by introducing a second consumer. Consumers reproduce only once per year, the resource reproduces throughout the “summer” season. When we use linear consumer reproduction between years, we find explicit expressions for the trivial and semi-trivial equilibria, and we prove that there is no positive equilibrium. When we use non-linear consumer reproduction, we determine conditions, for which both semi-trivial equilibria are unstable. We prove that a unique positive equilibrium exists in this case, and we find an explicit analytical expression for it. By linear analysis and numerical simulation, we find bifurcations from the stable equilibrium to population cycles and even chaos that may appear through period-doubling or Hopf bifurcations. We use mutual invasion analysis to find large regions in parameter space where the two consumer species can coexist. We interpret our results in terms of climate change that changes the length of the “summer” season.

# Stretching the Embryonic Lung Tissue May Affect the Length of its Epithelial Tubes

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In this talk, I present my recent findings on embryonic lung branching morphogenesis. The mammalian lungs develop through a repetitive process of dichotomous branching of its epithelial tissue. This process is coordinated by interactions between the lung epithelium and its surrounding mesenchyme [1]. The branching process is known to occur in three steps: an elongation phase where the branch grows toward the capsule, a stopping phase where the branch ceases to elongate and a branching phase where the branch divides in two. In tracheal occluded lungs, the stopping distance at which the branches cease to elongate decreases by 50% and causes the branches to be closer to the capsule [2]. Why the stopping distance decreases in tracheal occluded lungs remains unknown. We developed a novel method to study lung branching in tracheal occluded lungs. The method uses a computational model to describe key molecular players and lung tissue mechanics occurring in tracheal occluded lungs. The epithelium is modeled as an elastic solid and molecular interactions is modeled using the partial differential equation. I will present simulation results that show that tracheal occlusion changes the shape of the epithelial tube and affects the localization of key morphogens. I will also discuss why the changes in morphogen localization results in a decrease in the stopping distance.

**Subdiscipline area:** Developmental Biology

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# Investigating the effect of domain growth on the collective migration of neural crest cells

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Collective neural crest (NC) cell migration determines the formation of peripheral tissues during vertebrate development. If NC cells fail to reach a target or populate an incorrect location, improper cell differentiation or uncontrolled cell proliferation can occur. Therefore, knowledge of embryonic cell migration is important for understanding birth defects and tumour formation. However, the response of NC cells to different stimuli, and their ability to migrate to distant targets, are still poorly understood. It has been proposed that cranial NC cells may undergo directed movement in response to a cell-induced chemoattractant gradient. The migration of NC cells occurs on a growing domain and, previously, it has been assumed that the domain grows uniformly in space. However, there is no experimental evidence for uniform growth, leaving open the question of the effect of different domain growth profiles on the migration of NC cells.

We develop and apply a modelling framework to analyse the effect of different types of domain growth on NC cell invasion. We consider different non-uniform growth profiles and investigate their effects on cell invasion using an off-lattice individual-based model for the cell population and a reaction-diffusion model to describe chemoattractant dynamics. Our results reveal that the domain growth profile has a significant effect on NC cell invasive abilities. We investigate a number of possible growth profiles and determine how efficient they are at enabling successful cell invasion. These results suggest further avenues of experimental research.

## How mathematical modeling of *Trypanosoma brucei* population dynamics in mice can test hypotheses for parasites growing in adipose tissue versus blood

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The adipose tissue is a large reservoir for *Trypanosoma brucei* in mice. In this environment, adipose tissue forms (ATFs) rewire their gene expression and activate fatty acid catabolism. How a large reservoir of functionally distinct parasites contributes to the dynamics of parasite load in the host remains unknown. In this study, we mathematically modeled the number of parasites and the proportion of transmissible forms in blood and adipose tissue during infection. In a system of ordinary differentially equations, fitted to the infection data, we tested several hypotheses for trait differences between compartments, including parasite growth, differentiation and migration between tissues. One model that fits well our data suggests that in the adipose tissue parasites grow about 50% more slowly than in the blood. To test this model, additional biological evidence was sought, comparing the proteomes and cell cycles of parasites isolated from the blood and adipose tissue. These analyses revealed lower replication potential of parasite of ATFs and a reduced protein synthesis compared to their bloodstream counterparts, thus confirming the predictions of the mathematical model. Slow-growing parasites in particular compartments create within-host heterogeneity, which may help reduce disease severity and contribute to asymptomatic disease described in the field.

Keywords: Population dynamics, Ecology and Evolution

## Modelling the Herding of Garrano Horses in the Wild

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Many species in the animal kingdom aggregate to keep a group cohesive. Some of these groupings are autonomous such as in flying birds, while others are controlled by a specific individual such as a shepherd dog or a harem stallion. In this work, we propose a mathematical model of herding of a group of female horses by a harem stallion, which is a modification to that of sheep by a shepherd dog. To do this, we recorded the herding behaviour of feral horses (*Equus caballus*) in Northern Portugal using unmanned aerial vehicles (or drones) and applied image processing techniques to track their positions. In our model, a female horse moved in the direction of a linear combination of the following six components: inertia, a repulsive force from the stallion, a long-range attractive force, a short-range repulsive force, a force of synchronisation, and an attractive force to the centre of the group. The coefficients were then estimated from the recorded data. Our results showed that our model explains the data well.

# The effects of metapopulation dispersal theory on Columbia spotted frog population dynamics

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Presented by Guen Grosklos

Recent reports show global declines in amphibian populations spurred by climatic variation and pond habitat structure. Theoretical models have investigated the impacts of climate (mean snowpack, runoff, etc.) and pond heterogeneity (diversity of pond depths) on amphibian populations, but little work has been done on how population dynamics are affected by dispersal between ponds. In metapopulation theory, dispersal rates can either stabilize or destabilize metapopulation dynamics in a stochastic environment. We apply metapopulation theory to previously developed stage-structured matrix models of the Columbia spotted frog (*Rana luteiventris*) by incorporating dispersal between ponds at a known Columbia spotted frog breeding site. We show that Columbia spotted frog growth and extinction rates are affected by inter-pond dispersal. In particular, moderate rates of dispersal can increase population growth rates while mitigating extinction rates. However, exceptionally high dispersal rates can cause extinction rates to be higher than if there were no dispersal. Understanding the effects of dispersal rates provides insight into effective management strategies for maintaining Columbia spotted frog habitats and the underlying causes of spotted frog population declines.

## MULTI-RESOLUTION MODELLING IN MOLECULAR DYNAMICS

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Molecular dynamics (MD) approaches, based on the rules of classical mechanics, have been used to study the behaviour of complex biomolecules in biological applications, such as DNA-protein interactions and drug discovery.

Biologically relevant simulations have to be done in aqueous solutions, and a number of water models have been developed in the literature to use in all-atom MD simulations and coarse-grained MD models. We consider two theoretical heat baths which enable further analytical progress than solvent models based on all-atom or coarse-grained water models [1]. The solvent particles which make up the heat bath interact with the monomers of the dimer either through direct collisions (short-range) or through harmonic springs (long-range). Two types of multi-resolution methodologies are considered in detail: (a) describing parts of the solvent far away from the dimer by a coarser approach; (b) describing each monomer of the dimer by using a model with different level of resolution. These methodologies are then used to investigate the effect of a shared heat bath versus two uncoupled heat baths, one for each monomer. Furthermore, the validity of the multi-resolution methods is discussed by comparison to dynamics of macroscopic Langevin equations, with convergence to these descriptions established in certain limits.

We extend these results to cases where memory effects play a larger role by using a generalised Langevin model as our means of coarse graining. This allows the use of kernel estimation techniques to set our model parameters based on detailed MD simulations employing more realistic water models.

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## Non-Equilibrium Dynamics in Under-Saturated Communities

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The concept of the evolutionarily stable strategy (ESS) has been fundamental to the development of evolutionary game theory. It represents an equilibrial evolutionary state in which no rare invader can grow in population size. With additional work, the ESS concept has been formalized and united with other stability concepts such as convergent stability, neighborhood invasion stability, and mutual invisibility. Other work on evolutionary models, however, shows the possibility of unstable and/or non-equilibrial dynamics such as limit cycles and evolutionary suicide. Such “pathologies” remain outside of a well-defined context, especially the currently defined stability concepts of evolutionary games. Ripa et al. (2009) offer a possible reconciliation between work on non-equilibrial dynamics and the ESS concept. They noticed that the systems they analyzed show non-equilibrial dynamics when under-saturated and “far” from the ESS and that getting “closer” to the ESS through the addition of more species stabilized their systems. To that end, we analyzed three models of evolution, two predator-prey models and one competition model of evolutionary suicide, to see how the degree of saturation affects the stability of the system. In the predator-prey models, stability is linked to degree of saturation. Specifically, a fully saturated community will only show stable dynamics, and unstable dynamics occur only when the community is under-saturated. With the competition model, we demonstrate it to be permanently under-saturated, likely showing such extreme dynamics for this reason. Though not a general proof, our analysis of the models provide evidence of the link between community saturation and evolutionary dynamics. Our results offer a possible placement of these unstable and non-equilibrial dynamics into a wider framework. In addition, the results concur with previous results showing greater evolutionary response to less biodiversity and clarifies the effect of extrinsic vs. intrinsic non-equilibrial evolutionary dynamics on a community.

## Identifying unique observations dSTORM with a spatiotemporal model

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Direct stochastic optical reconstruction microscopy (dSTORM) is a super-resolution technique that uses photoswitchable fluorophores to achieve resolutions at or below 20nm. A downside of dSTORM is the possibility of recording several blinks from one fluorophore, affecting the estimation of the number of molecules detected in the image. I constructed a mathematical model to identify unique fluorophores in dSTORM images by independently using the localization and the time series of the observations. The temporal sequence is described with a Markov chain approach and the spatial distribution is described with a Gaussian mixture model. To estimate the parameter values, I implemented a maximum likelihood procedure which requires a mixed (continuous-discrete) optimization. I have tested my protocol on simulated data and well-characterized DNA origami data. I further demonstrate the algorithm by removing extraneous localizations from dSTORM images of B-cell surface receptors. The distribution of B-cell receptors on the membrane is an important factor modulating B-cell activation. My model enhances a microscopy technique that is already widely used in biological applications and supports a deeper analysis of immune cells signaling.

# Seasonal influenza in England: Modelling approaches to capture immunity propagation

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Seasonal influenza poses serious problems for global public health, being a significant contributor to morbidity and mortality. In England, there has been a long-standing national vaccination programme, with vaccination of at-risk groups and children offering some protection against infection. Transmission models have been a fundamental component of analysis informing the efficient use of limited resources. However, these models generally treat each season and each strain circulating within that season in isolation.

We present a multi-strain, non-age structured SEIR-type transmission model for influenza incorporating mechanisms linking prior season epidemiological outcomes to immunity at the beginning of the following season. Amalgamating multiple sources of epidemiological and vaccine data for England covering the last decade, we perform parameter inference via Approximate Bayesian Computation methods to assess strain transmissibility, the strength of dependence prior season vaccination and disease status has upon immunity in the following season, and variability in the influenza case ascertainment across seasons. Parameter fits elicit susceptibility to a given strain type in the next season being modulated more heavily if naturally infected by that strain type in the current season, compared to residual vaccine immunity. In addition, analysis of a counterfactual non-vaccination scenario reveals alterations to the predicted circulating strain composition.

To conclude, we outline steps to augment the transmission model with age structure, and interface with economic evaluation frameworks for appraising cost-effectiveness of prospective seasonal influenza vaccination programmes.

## Product-Form Stationary Distributions for Non-Complex Balanced Networks

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In many biochemical reaction networks, the number of molecules of each species in the network is low. Because it leads to large fluctuations in the system, a stochastic model is commonly used to understand such networks with a low number of molecules. The stochastic model describes the dynamics of the distribution of the number of molecules using the chemical master equation (CME). While solving CME analytically is nearly impossible in the presence of nonlinear reactions, recent studies have found that such calculation is possible for special types of networks such as feedforward loop and complex balanced network. In this talk, I will introduce a more general class of networks whose stationary distribution can be derived analytically. Furthermore, using this approach, I will illustrate how the exact stationary distributions of various systems such as SIS model, the dimerization models, and the duplication model can be easily derived.

# Analyzing the Sleep Patterns of Shift Workers using the neuronal population model of sleep-wake cycle

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While shift workers suffer from excessive daytime sleepiness and insomnia, the cause of daytime sleepiness and insomnia remains unclear. To identify such cause, we analyzed complicated sleep patterns of 23 nurses on a rotating shift schedule collected for 14 days from Samsung hospital. For this, we use an established neuronal population model of the sleep-wake cycle which includes mutual inhibition between wake-promoting and sleep-promoting neurons, as well as drive consisting of circadian rhythm and the homeostatic sleep pressure. This analysis leads to the development of a new index called Sufficient Sleep Percentage (SSP) which is the first index to predict daytime sleepiness and insomnia of shift workers from their sleep patterns. This shows how the mathematical model can be used to provide optimal sleep-wake schedules to improve sleep qualities of shift workers.

# Patient-specific, predictive modeling of the response to chemoradiation via MRI

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**Introduction:** Despite receiving aggressive standard-of-care therapy, patients with high grade gliomas have an overwhelmingly poor prognosis that typically includes recurrent or progressive disease following completion of chemoradiation. A fundamental challenge in patient care in neuro-oncology (and oncology in general) is accurately predicting response following completion of therapy. Predictive mathematical models calibrated by patient-specific quantitative imaging measures could facilitate predicting a patient's response in a timely manner and thus enable personalized, adaptive treatment regimens. Towards this end, we have developed a 3D mathematical model of tumor growth and response which can be completely parameterized from patient-specific imaging data. In particular, the model captures subclinical and clinical disease spread following chemoradiation therapy. In this report, we evaluate the predictive accuracy of this model in a preliminary study of two patients with high grade gliomas receiving standard of care therapy.

**Methods:** Our preliminary dataset includes two patients who were imaged at baseline (prior to chemoradiation), 1 month following chemoradiation, and then again at 3 months following chemoradiation. Patients received standard of care radiation therapy (60 Gy over 30 fractions) concurrently with temozolomide. Adjuvant temozolomide was continued up to 6 cycles post-RT.  $T_2$ -FLAIR, diffusion weighted MRI (DW-MRI), and post-contrast  $T_1$ -weighted images were collected at each visit. The clinical (or bulk) and sub-clinical (or infiltrating) tumor regions were expertly segmented from the post-contrast  $T_1$ -weighted and  $T_2$ -FLAIR images, respectively. Within the clinical tumor regions, we assigned tumor cell number using the apparent diffusion coefficient estimated from DW-MRI [1]. Within the sub-clinical regions, we linearly interpolated the tumor cell number from 2% of the carrying capacity (at the periphery of the tumor region) to the number of tumor cells calculated at the periphery of the clinical tumor region [2]. Tumor growth and response to chemoradiation was modeled using a 3D mechanically-coupled reaction-diffusion model [3] describing the spatiotemporal evolution of tumor cell number due to proliferation, diffusion, death due to chemoradiation. Patient-specific model parameters were calibrated using cellularity estimated from the first two visits. The calibrated parameters were then used in a forward evaluation of the model to predict the tumor growth observed at the 3<sup>rd</sup> visit.

**Analysis and Conclusion:** A strong level of correlation (Pearson correlation coefficients > 0.68) and agreement (concordance correlation coefficients > 0.71) was observed between the predicted and estimated cellularity at the third visit in both patients. Similarly, a strong level of spatial agreement was observed with Dice coefficients greater than 0.61 for the subclinical ( $T_2$ -FLAIR regions) and greater than 0.72 for the clinical (post-contrast  $T_1$ -weighted images). This preliminary study demonstrates the potential of incorporating patient-specific imaging data into predictive mathematical models. Future directions include incorporating drug-specific mechanisms and modeling edema.

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## **B. Title and Abstract.**

**Title:** Understanding the role of neutrophils in *M. tuberculosis* infection: Modeling approaches and visualization techniques

**Authors:** Caitlin Hult, Joshua T. Mattila, Jennifer J. Linderman, Denise E. Kirschner

### **Abstract:**

Gaining a better understanding of the immune response to infection with the bacteria *Mycobacterium tuberculosis* (Mtb) is crucial to help combat the increased prevalence of multi-drug resistant strains, the current complexity and length of treatment, and the inherent difficulties of experimental work. Computational modeling 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, particularly with regard to the role of neutrophils in Mtb protection versus pathology. Due to the duration and dynamic nature of this response, coupled with the involvement of immune processes that occur over tissue, cellular, and molecular scales, we take a multi-scale and mechanistic computational modeling approach. We build an agent-based model at the cellular scale which produces output at a tissue scale that incorporates mathematical elements including diffusion and recruitment, and we use a middle out approach to make this model multi-scale by adding molecular scale dynamics. Through the incorporation of a neutrophil cell type into this hybrid agent-based computational model, *GranSim*, we investigate the spatiotemporal dynamic formation of lung granulomas in response to Mtb infection. We present a neutrophil-inclusive computational model that is able to reproduce experimental results as seen in temporal CFU counts, cell counts, and IHC images. We generate simulated granulomas whose range of spatial configurations reflects the heterogeneity observed experimentally, and through identification of parameters that drive such heterogeneous outcomes, we aim to improve our understanding of how and if neutrophil behavior influences the success of the immune response to Mtb infection. Through the parallel development of a 3D version of *GranSim*, we analyze simulated output in 2D and 3D environments, and we present novel 3D visualization techniques to enhance conceptual understanding of the immune environment and granuloma formation.

## Equivalences Between Age Structured Models and Distributed Delay Differential Equations

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By solving along the characteristics age-structured PDE models often result in delay terms in differential equation (DDE) models. If the aging velocity is constant and the maturation age is fixed then a constant discrete delay results. However, in many situations either the maturation rate is variable, or the maturation age itself is randomly distributed. It is then very easy to write down an incorrect DDE. We show how to derive appropriate DDEs in both situations. In the case of variable aging velocity and randomly distributed maturation age we demonstrate how the resulting state-dependent distributed delay DDE can be recast as an ODE using a generalisation of the linear chain technique. We will also discuss the limiting process as the probability density function approaches a delta function and the distributed delay DDE approaches a discrete DDE in a surprising manner.

## Eliminating stage-structured pests with temperature-dependent life histories

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Mathematical modelling to understand population stage structure is useful to predict the abundance of hard-to-measure life stages, and to determine the efficacy of management strategies that target specific life stages. However, for most ectotherms, fecundity, maturation, and mortality rates are temperature-dependent, and so stage structure will vary with regional and seasonal differences in temperature. I use a delay differential equation model describing the population dynamics of salmon lice, a stage-structured marine copepod, to motivate a general exploration of temperature-driven stage-structured population dynamics, and the implications for pest control. I find that in cold conditions, which induce diapause, the salmon lice population is dominated by the adult stage, and this bottlenecked stage structure provides a unique opportunity to potentially eradicate the population with the least amount of effort.

## A General 'Linear Chain Trick' for building ODE models with flexible dwell times

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ODE models are widely used state transition models that are often thought of as mean-field equations for an underlying stochastic model. In that context, they typically (implicitly) assume an individual's dwell time in a given state is exponentially distributed (or more generally, follows a Poisson Process 1st event time distribution). Consequently, ODEs have been criticized for this inability to incorporate other dwell-time distributions. The Linear Chain Trick (LCT; aka the Gamma Chain Trick) is a technique for constructing mean field ODE models with dwell times that are Erlang distributed (i.e., gamma distributed with integer shape parameter), however we lack general theory to facilitate the easy application of this technique, especially for complex models, and ODEs must instead be derived from integral equations and/or continuous time stochastic models. This shortcoming has forced modelers to choose between constructing ODE models using heuristics with oversimplified dwell time assumptions, using time consuming derivations from first principles, or to instead use non-ODE models (like integro-differential equations or delay differential equations) which can be cumbersome to derive and analyze.

In this talk, I will present analytical results that generalize the LCT, and should enable modelers to more efficiently construct mean field ODEs that better incorporate appropriate dwell time assumptions, including some conditional dwell time assumptions. Specifically, I will 1) present novel extensions of the LCT to various scenarios found in applications; 2) provide formulations of the LCT and its extensions that bypass the need to derive ODEs from integral or stochastic model equations; and 3) I'll introduce a novel Generalized Linear Chain Trick (GLCT) framework that extends the LCT to a much broader family of distributions, including the flexible *phase-type* distributions. These results also help clarify connections between individual-level stochastic model assumptions and the structure of corresponding mean field ODE models.

### Subdiscipline Area:

- Population Dynamics, Ecology and Evolution
- Mathematical Epidemiology

## Toward a New Theory of Biological Information

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Many attempts have been made to understand biomolecular machines, such as the ribosome, from a computational and information-theoretic perspective. However, it is well-understood that current information theory is limited to symbolic (i.e., syntactic) manipulations only and is not equipped to deal with objects that possess functions beyond such manipulations. We present a quantitative analysis of the information-processing abilities of several classes of biomolecular machines that demonstrates their capacities for biological information. Furthermore, we argue that such machines possess functions that lie beyond the scope of traditional Shannon information theory and require a new description to completely characterize them. Finally, we propose new ways to extend current models by rigorously abstracting the structure and dynamics of these machines.

Identifying the dominant transmission pathway in a multi-stage infection model of the emerging fungal pathogen *Batrachochytrium salamandrivorans* on the Eastern Newt

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Epidemic dynamics of infectious diseases with multiple routes of transmission are complex. Mathematical models can be used to determine invasion potential and identify which transmission pathway is dominant and can ultimately help identify appropriate intervention strategies. We developed compartmental host-pathogen models to examine the transmission dynamics of an emerging fungal pathogen on an amphibian population. Multiple stages of infection are incorporated into the model, allowing disease-induced mortality and zoospore shedding rates to vary as the disease progresses. Parameter sensitivity analysis shows that the recovery rate and environmental zoospore degradation rates are influential parameters. Calculation of the basic reproductive number ( $\mathcal{R}_0 > 7$ ) highlights the virulence of this pathogen and is used to determine that direct transmission is the dominant transmission pathway for small population densities, while environmental transmission dominates in large populations.

## Inference of an Inflammatory Cytokine Interaction Network

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Cytokines are the messenger molecules of the immune system. They are an important therapeutic target in immune mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). Inhibition of the inflammatory cytokine TNF has transformed the treatment of RA and other IMIDs and has led to the development of various other anti-cytokine therapies. Cytokines interact in a tightly regulated network and depending on the context a particular cytokine can be protective or inflammatory. In order to determine which cytokines to target in specific disease types and patient subsets, it is critical to study the effects of the inhibition of one or more cytokines on the larger cytokine interaction network. We study the production of various cytokines that are produced by peripheral blood mononuclear cells in inflammatory conditions ( $n=17$  healthy donors). Cytokine production by monocytes of six relevant cytokines is measured by flow cytometry in the presence and absence of 25 different cytokine(receptor) inhibitors ( $n=52$  different combinations examined). We infer possible direct cytokine interactions from the data by statistical analysis and enumerate all possible network configurations based on this initial set of network edges. Each network configuration is modelled by a system of ordinary differential equations and fitted to the experimental dataset. We rank the different network configurations based on their fit to the data, using the Bayesian information criterion and Akaike information criterion. We repeat the network extraction process while considering a much larger set of network configurations consisting of all possible positive and negative interactions between all cytokines, i.e. we do not constrain the possible edges to the statistically significant set of edges as we did before. We compare the optimal networks resulting from both approaches. The two extracted networks enable us to study indirect cytokine interactions and to quantify the effect of cytokine inhibition. The networks are also used to predict the combined effects of inhibiting various cytokines simultaneously.

**Subdiscipline area:** Immunobiology and Infection.

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## Model-Based Analysis of Recovery of Gut Microbiota after Antibiotic Disturbance

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We consider anaerobic digestion in the human colon using a mathematical model for a complex bacterial population in a continuous stirred tank reactor (CSTR) with a lateral diffusion compartment representing the mucus layer of the intestine. This model considers the digestion of carbohydrates into short chain fatty acids (SCFAs) and gas by a microbial community, incorporating metabolic process, transport phenomena and external transport to the host. It is an adaptation and extension of the carbohydrate degradation model presented in [1]. To encompass the diversity in the gut, the microbial community is represented by four biomass functional groups (BFGs) which are further divided into subgroups. In its basic form, the resulting model consists of 28 ordinary differential equations, more as the descriptions of the BFGs are refined.

Gut microbial communities display a large amount of interindividual variability in composition, however it has been found that a relatively stable state exists for an individual. Disturbances from homeostasis, which can occur through various means, have been implicated in the pathogenesis of many disorders. In particular, the administration of antibiotics has been found to cause a shift from the healthy equilibrium to a state with reduced species diversity, possibly permanently. We consider the impact of different antibiotic mechanisms and regimes on the reestablishment of equilibrium by considering the diversity of microbial species and concentration of SCFAs after perturbation. The effect of prebiotics, probiotics, and functional redundancy in BFGs on the recovery of equilibrium is also investigated.

[1] Muñoz-Tamayo et al. (2010) J Theor Biol 266(1):189-201

## Fire Mediates Bark Beetle Outbreaks in Serotinous Forests

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Bark beetle outbreaks and forest fires have imposed severe ecological damage and caused billions of dollars in lost resources in recent decades. These disturbances are projected to become more severe as climate change takes its toll on our forest ecosystems. Here, we investigate the impact of multiple disturbances in a demographically heterogeneous tree population, using an age-structured difference equation model of bark beetle outbreaks and forest fires. We identify four distinct dynamical regimes for beetle and fire dynamics. The model predicts that fire helps dampen beetle outbreaks not only by removing host trees but also by altering the demographic structure of forest stands. Furthermore, a stand thinning protocol that reduces the size of the largest few juvenile classes in a stand by only a small percentage (5% - 15%) can significantly reduce beetle-induced tree mortality, and increase mature populations, in certain regimes. Forests will be subject to new environmental regimes involving multiple disturbances in the coming decades, and we have illustrated one approach to integrating multiple disturbances in a mathematical model in order to anticipate how forests might respond.

## Mathematical Modeling to Reveal Molecular Differences Causing Pacemaker-neuron-dependent Rhythm Alteration by Mutant

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Circadian ( 24h) behavior of Drosophila is regulated by about 150 pacemaker neurons. In each pacemaker neurons, to generate and maintain 24h rhythm, circadian gene expression is driven by transcriptional-translational feedback loop (TTFL). Although all of TTFLs in each pacemaker neurons based on negative feedback between activator and repressor, molecular rhythms are altered differently when repressor binding to activator is disrupted by mutant; for oscillation of repressor protein, amplitude is largely reduced in one neuronal group, but not in another neuronal group. To investigate this unexpected phenomenon, we established the mathematical model based on mass action kinetics. By analyzing conditions which the model generates rhythm, we predicted the difference of molecular composites of two neuronal groups causing pacemaker-neuron-dependent rhythm alteration. This prediction is confirmed by the follow up experiment. Our work shows that clockworks at the molecular level have a critical role for rhythm generation of each pacemaker neurons.

## Controlled Switched System for Cancer Model

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We investigate a simple mathematical population model of tumor and non-tumor interactions where the application of chemotherapy is considered as a control variable. The feature thing in this work is that the control variable is not considered continuous by time but piecewise-continuous which is introduced in our work by an impulsive control. This kind of control is motivated by the fact that chemotherapy is not applied continuously (day by day treatment) but piece wisely continuous (a break between two chemotherapy applications). Furthermore, we study an optimal control problem to find the best strategy to minimise the number of tumor cell which mean maximising health state of the treated person. We discuss also numerical results for chemotherapy regimens.

## The influences of host evolution on host-pathogen interactions across space

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Current evolutionary studies of host-pathogen dynamics usually consider either pathogen evolution alone or host-pathogen coevolution due to the relative generational timescales. However, for some diseases (e.g., White Nose syndrome in bats), there is evidence that hosts may actually be evolving more rapidly than the pathogen. In these cases, spatial, temporal, evolutionary, and epidemiological factors may all drive eventual dynamics. To study such systems, we consider the case of one pathogen introduced into a population of hosts with two genotypes: wild type and robust, which differ from each other only in the mortality rate from pathogen infection. We employ a classic SI model and explore the host-pathogen dynamics in one population. We then extend our study to consider the spatial structure of hosts in multiple patches to discover how the equilibria of host genotypes might change as a function of the relative mortality of the different genotypes and the host migration patterns among patches. We show that although in one patch the hosts with robust genotype or large initial value gradually dominates the system, in a multiple-patch system migration of the frequency of wild type hosts should be expected to increase when disease-driven mortality is relatively low but decrease when disease-driven mortality is high. The above influence of migration is stronger when the patches are less connected. This study reveals the potential synergistic effects of both epidemiology and metapopulation ecology on host-pathogen evolutionary dynamics in cases where the disease acts as a sudden selective pressure on host survival, and therefore has profound implications for the understanding and management of novel invasive pathogens.

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B. Title And Abstract: An integrated approach to calibrate and validate mathematical models of therapy-induced resistance from in vitro drug response data in cancer

The development of resistance to chemotherapy is a major cause of treatment failure in cancer. Intratumoral heterogeneity and phenotypic plasticity are known to play significant roles in drug resistance. The contribution of therapy-induced resistance is an area of increased interest as it has direct consequences for the optimization of treatment protocols. To elucidate the mechanistic roles of heterogeneity and plasticity in chemotherapy resistance, therapeutic response should be evaluated using both phenotypic characterization and bulk population dynamics. However, integrating multiple data types into a comprehensive mathematical modeling framework has remained a challenge in the field. In this work, we develop an integrated mathematical-experimental approach to calibrate and validate a model of drug-induced resistance. In order to see under the hood and understand the molecular underpinnings of drug response dynamics, we utilize recent advances in single cell RNA sequencing and single cell lineage tracing to better understand the molecular underpinnings of the drug response at the individual cell level. Using lineage tracing to track clonal dynamics, we are able to identify the fate of resistant and sensitive subpopulations and characterize the gene expression states associated with chemotherapy resistance. Using principle component analysis, we can classify cells from downstream post-treatment time points into sensitive and resistant states to obtain estimates of the phenotypic composition of the cancer cell population over time. The phenotypic composition dynamics are combined with longitudinal drug response dynamic data and calibrated to a mathematical model of drug-induced resistance. We validate the model by comparing model predictions of repeat treatments at different time intervals to experimental observations of subsequent treatments. This framework is the first work to our knowledge that combines time-resolved single cell RNA sequencing and lineage tracing data with mathematical modeling to reveal the dynamics of drug-induced resistance.

C. Discipline Area: Mathematical Oncology

## Struggle for Existence: models for Darwinian and non-Darwinian selection

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Classical understanding of the outcome of the struggle for existence results in the Darwinian “survival of the fittest”. Here we show that the situation may be different, more complex and arguably more interesting. According to Gause (1934), “All populations have the capacity to grow exponentially under ideal conditions, and no population can grow exponentially forever – there are limits to growth. This generates the Malthusian Struggle for Existence”. One may recognize here the description of logistic population model; the inhomogeneous logistic equation presents a simplest conceptual model for Darwinian Struggle for Existence. Here we show that this model in general does not generate the Malthusian struggle for existence and survival of the fittest. Specifically, we show that different versions of inhomogeneous logistic-like models with distributed Malthusian parameter imply non-Darwinian “survival of everybody”. In contrast, the inhomogeneous logistic equation with distributed carrying capacity shows Darwinian “survival of the fittest” that correspond to the maximal carrying capacity. We also consider an inhomogeneous birth-and-death equation and give a simple proof that this equation results in the “survival of the fittest”. In addition to this known result, we find an exact limit distribution of the parameters of this equation that gives a complete description of all the “fittest” individuals. We also consider “frequency-dependent” inhomogeneous models and show that although some of these models show Darwinian “survival of the fittest”, there is not enough time for selection of the fittest species. We discuss the Gause’s Competitive exclusion principle that was formulated by Hardin (1968) as “Complete competitors cannot coexist”. While this principle is often considered as a direct consequence of the Darwinian “survival of the fittest”, we show that from the point of view of developed mathematical theory complete competitors can in fact coexist indefinitely.

## Dynamics of Gene Regulatory Circuits Drive Irreversible Transitions of Cell Cycle

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Complex biological processes, such as cell cycle, usually involve precise cellular state transitions controlled by gene regulatory circuits. Typical genomic approaches measure data for snapshots of cellular states but provide little insight into their dynamics. Here, we used cell cycle as a model system to elucidate its state transitions using a systems biology approach. We applied our recently developed mathematical modeling algorithm, named random circuit perturbation (RACIPE), to the core cell cycle gene regulatory circuit of 15 genes. RACIPE takes the topology of the gene regulatory circuit as the only input, and generates an ensemble of ODE models with distinct random kinetic parameters. The modeling results from the ensemble of models are then subject to statistical analysis to identify robust feature of the gene regulatory circuit. Using RACIPE, we found that random models of the cell cycle circuit allow both stable steady states and limit cycles. The steady states can be clustered into six distinct groups that are associated with specific cell cycle phases. The time trajectories of limit cycles usually travel through the gene expression space of multiple cell cycle phases. We found that the limit cycles spanning four or more cell cycle phases are predominantly unidirectional along the cell cycle direction. However, the limit cycles spanning three or fewer phases exhibit random directions. These findings suggest that the steady states from random models can be associated with cell cycle phases, while the limit cycles control the directionality of the state transitions. We further explored the mechanism of the irreversible state transitions of cell cycle by examining how cells transit between models from one state or another. These results demonstrate that the ensemble-based modeling approach and the related statistical data analysis framework elucidates the dynamics of cell cycle state transitions. The approach is applicable to gene regulatory circuits of other biological processes.

## Self-organized Division of Labor Leads to Behavioral Contagion in Mixed Social Groups

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From microbes to humans, social groups at different biological scales divide tasks among specialized individuals. The emergence of such division of labor is a major transition in the evolution of social organization and considered a key to the ecological success of many social groups, especially social insect colonies. Theory suggests that interindividual variability in response thresholds among workers that are otherwise identical can generate specialized behavior. However, few studies consider interactions between individuals with distinct behavioral tendencies that are genetically or developmentally determined. Even fewer directly link theory and experiment.

We combine computational and analytical modeling with experimental data to investigate fixed thresholds, the simplest form of response thresholds, as a mechanism for the emergence of specialized behavior in genetically or developmentally heterogeneous groups. These groups exhibit different behavioral types that differ in the efficiency with which they perform tasks and in the ability to meet the needs of the colony. Counterintuitively, in the fixed threshold model, we find that mixing two types of individuals that differ in task performance efficiency results in behavioral contagion, whereby the types become behaviorally more similar to each other when mixed. Moreover, this contagion exhibits asymmetry that depends on how well each type can keep up with the demands of the colony. We then compare our theoretical results with experimental data from camera tracking experiments in colonies of the clonal raider ant, *Ooceraea biroi*, with controlled variations in genetic, demographic, and morphological types. We find that the fixed threshold model can capture the range of behavioral patterns observed in these colonies. Finally, we extend the model to predict the average behavior of colonies with varying ratios as well as numbers of behavioral types. This work demonstrates that fixed thresholds, despite their simplicity, offer a powerful mechanism to capture and predict the emergence of social organization in heterogeneous groups.

## A Mathematical Model of Thrombin-Fibrin Binding

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Thrombin is an enzyme generated during the blood coagulation process and is crucial to the formation of a stable blood clot. In particular, thrombin cleaves fibrinogen into fibrin, which polymerizes to form a stabilizing gel matrix. Thrombin can also be strongly sequestered by the fibrin matrix by binding directly to it after it is formed, but the binding mechanism is poorly understood. Recently, it was shown that thrombin can stay bound to a fibrin matrix for very long periods of time and is resistant to removal by flow and chemical inhibitors. A mathematical model describing a one-step binding event between thrombin and fibrin does not support these data. Thrombin binding to fibrin is truly bivalent, and occurs in two steps, but this notion has not yet been incorporated into a mathematical model. In this work, we show that mathematical models based on the one-step and two-step binding schemes can both produce prolonged thrombin binding to fibrin, but with different kinetic rates between the models and, in the case of the one-step model, different from experimentally measured rates as well. During the process of validating the models against experimental data, it was found that the model must necessarily include an intra-fiber, physically-trapped thrombin population. This hypothesis was supported by calculations of the average distance between fibrin protofibrils. Further, we show how the two-step model, but not the one-step model, can be used to study anticoagulant drugs specific to thrombin.

## Marine Reserves and Optimal Dynamic Harvesting When Fishing Damages Habitat

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Marine fisheries are a significant source of protein for many human populations. In some locations, however, destructive fishing practices have negatively impacted the quality of fish habitat and reduced the habitat's ability to sustain fish stocks. Improving the management of stocks that can be potentially damaged by harvesting requires improved understanding of the spatiotemporal dynamics of the stocks, their habitats, and the behavior of the harvesters. We develop a mathematical model for both a fish stock as well as its habitat quality. Both are modeled using nonlinear, parabolic partial differential equations, and density-dependence in the growth rate of the fish stock depends upon habitat quality. The objective is to find the dynamic distribution of harvest effort that maximizes the discounted net present value of the coupled fishery-habitat system. The value derives both from extraction (and sale) of the stock and the provisioning of ecosystem services by the habitat. Optimal harvesting strategies are found numerically. The results suggest that no-take marine reserves can be an important part of the optimal strategy and that their spatiotemporal configuration depends both on the vulnerability of habitat to fishing damage and on the timescale of habitat recovery when fishing ceases

# The evolutionary forces acting on prophages: A mathematical study

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Prophages, viral genetic sequences carried within bacterial genomes, are the main source of genetic variation in bacteria [1], and contribute to both bacterial virulence and antibiotic resistance. Thus, prophages have critical public health implications. After integration in the bacterial genome (lysogeny) prophage are subject to [2]:

- Degradation: A random mutational process that can degrade the intact prophage.
- Induction: Prophage can excise from the bacterial genome, spontaneously or in response to some external stimuli, and kill the host bacterial cell.
- Selection: Benefits conferred by prophages can increase the proliferation of their bacterial hosts.

We have developed a PDE model to quantify the effects of these forces on the distribution of prophages within bacterial genomes, and fit the model to three recent data sets, predicting the relative magnitudes of these effects in maintaining prophage sequences. We have also carried out gene-level simulations to elucidate the effects of these processes on the genetic composition of prophages. Our preliminary results indicate that prophage sequences should be enriched for sequences that are beneficial for bacteria but, surprisingly, may not preferentially lose the genes required for lysis. We compare these model predictions with a bioinformatics analysis of proteins of known function in prophage sequences identified in sequenced enterobacteria.

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## Force-Dependent Mechanics of Kinesin Molecular Motors

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**ABSTRACT.** Kinesins are molecular motors that transport cellular cargoes along microtubule filaments away from the cell center in neuronal and non-neuronal cells using chemical energy derived from the hydrolysis of ATP. Single kinesin motors are able to take hundreds of steps along a microtubule before detaching, which is essential to ensure that cellular cargoes are transported reliably over long distances. The defects in the kinesin-based transport contribute to numerous human diseases, such as Alzheimers, Parkinsons and cancer. While the mechanics of single kinesins are well characterized experimentally, the collective behavior of multiple kinesins varies considerably among experiments. These variations indicate that there is likely to be significant variations in conditions among the experiments, though the nature of these variations is not known. Here, we propose a theoretical framework that provides a novel interpretation for the recent single-motor force measurements: the vertical component of applied force accelerates the detachment of kinesin from microtubule, while the horizontal force component decelerates the detachment when the force resisting the motor. This directionality, together with the strength of intermolecular coupling, when applied to multiple motor assays, can account for the variation in the collective mechanics of multiple kinesins.

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## Systems model reveals the sources of the inter- and intraspecies variability in drug efficacy

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The majority of previous studies investigate the drug efficacy only in nocturnal species (e.g. mice) although humans are diurnal. Here, using diurnal monkeys, we examine the effect of a daily (circadian) clock-modulator drug, and find the high variability in its effect between diurnal monkeys and nocturnal mice. To identify the source of the interspecies variability, we used the systems pharmacology model, which accurately simulates the intracellular action of the drug and thus its effect in the circadian clock. This revealed that the interspecies variability in the drug effect is due to the different sensitivity of nocturnal and diurnal animals to environment light, the natural clock-modulator. Furthermore, via a combination of the model simulation and experiment, we found the molecular biomarker to predict the drug effect, which explains the high interindividual variability in the drug response. Based on these findings, we developed a model-based precision medicine strategy to treat circadian disruption. Our works show how the mathematical model can be used to reveal an unrecognized biological variable in drug efficacy translation between nocturnal and diurnal animals and enable precision medicine.

## Mathematical model and intervention strategies for mitigating tuberculosis in the Philippines

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Tuberculosis disease (TB) is one of the top 10 causes of death world wide. Million of people are suffering from TB disease. Two thirds of TB patients are in eight countries and 6% of patients are from the Philippines. TB is the sixth leading cause of morbidity and mortality in the Philippines. In this talk, a mathematical TB model fitted to the Philippine data is developed to understand its transmission dynamics. The optimal control strategies is also suggested for minimizing the number of high-risk latent and infectious TB patients considering implementation costs. Results suggest that enhancing active case finding control instead of case holding control together with distancing and latent case finding control is more effective to mitigate the spread of TB in the Philippines.

## Modeling the Stem Cell Hypothesis for Cancer

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Stem cell hypothesis proposes that the relapse of cancer, following chemotherapy is due to the presence of cancer stem cells. These slow-cycling cells are not targeted by chemotherapy and have the potential to initiate or sustain tumors. In this talk, we present a mathematical model for the interaction of immune system, cancer stem cells and tumor cells that incorporates the TGF- $\beta$  protein, secreted by the tumor and regulatory T-cells which acts as an immune suppressor. We investigate two cases: a no-treatment case, and one with chemotherapy and demonstrate the relapse of cancer even under aggressive chemotherapy. The parameters are fit to experimental data from the TC1 mouse model of cancer caused by the human papillomavirus.

## An observer for an occluded reaction-diffusion system with spatially varying parameters

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Spatially dependent parameters of a two-component chaotic reaction-diffusion PDE model describing ocean ecology are observed by sampling a single species. We estimate model parameters and the other species in the system by autosynchronization, where quantities of interest are evolved according to misfit between model and observations, to only partially observed data. Our motivating example comes from oceanic ecology as viewed by remote sensing data, but where noisy occluded data are realized in the form of cloud cover. We demonstrate a method to learn a large-scale coupled synchronizing system that represents spatiotemporal dynamics.

# Modified Metropolis-Hastings Algorithm for Efficiently Searching Parameter Space

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Mathematical models of biological processes frequently contain large number of free parameters to be determined. Existing methods for parameter search maybe very time-consuming and may fail to cover the true parameter space for complex biological models. We developed the new method called *Modified Metropolis-Hastings (MMH)* algorithm that efficiently produces a large number of parameter sets for any given model, with resulting parameter values covering large regions of parameter space.

MMH is a modification of classical Metropolis-Hastings Markov chain Monte Carlo algorithm, with different form of proposal probability density function and additional acceptance criterion based on ability of the proposed parameter set to satisfy user-chosen criteria of a given biological model. The algorithm is not required to converge to invariant distribution, and hence does not discard any parameter sets that are successful in terms of biological model criteria. This allows to produce a large number of successful parameter sets on a much shorter time scale in comparison to existing random search methods. We illustrated the performance of MMH versus several state-of-the-art algorithms on five biological models of increasing complexity, and we found that MMH outperforms these algorithms for all models, with a larger relative increase in performance for more complex models.

Resulting parameter sets represent a working parameter space for a model, and data analysis techniques can then be applied to extract essential features of the model parameters and make inference about model structure and behavior. We used linear and kernel machine learning methods for feature extraction from the parameter sets found by MMH algorithm, and our results agree with existing literature on the models of consideration.

## Dynamic Modeling Sheds Light on Links between Metal Uptake and Antibiotic Resistance in Plants

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Terrestrial plants extract minerals from the soil and in the process may take up antibiotics that are produced by soil microorganisms. To counteract the potentially adverse effects of these antibiotics, many plants have developed resistance mechanisms. In *Arabidopsis thaliana*, for instance, the *wbc19* gene confers resistance to the antibiotic kanamycin. While the exact mechanisms of this resistance are unknown, it was demonstrated that *wbc19* mutants are very sensitive to kanamycin. It turned out, at the same time, that their Zn uptake is compromised even in the absence of kanamycin but that Fe uptake in normal plants declines when they are exposed to kanamycin. These preliminary findings suggested a complicated link between antibiotics and the uptake of different metals. In this project, we investigate this link with a mathematical model that integrates metal homeostasis, especially of Fe and Zn, with the effects of kanamycin. The dynamic model is formulated as a Generalized Mass Action (GMA) system and calibrated with data generated obtained under various experimental conditions. Expanding on this calibration, large-scale Monte Carlo simulations are performed to determine ensembles of model instantiations that are consistent with the experimental results and within biologically acceptable parameter ranges. The modeling approach is hoped to shed light on the system of metal uptake and antibiotic resistance. Models such as this are also excellent tools for introducing undergraduate biology students to quantitative thinking and, thus systems biology. Specifically, they can serve as the basis for hands-on, computer-aided problem-based exploration and learning.

## Stochastic amplification of gene oscillations during embryonic neurogenesis

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The control and downstream interpretation of gene expression dynamics is crucial in many biological contexts. For example, gene expression oscillations have been proposed to control the timing of cell differentiation during embryonic neurogenesis. Here, we mathematically model novel data of oscillatory gene expression dynamics in mouse embryonic spinal cord tissue. By combining mathematical modelling and quantitative experimental data we show that these dynamics can be understood as a result of stochastic amplification, where oscillations are enhanced by intrinsic noise. We show how such oscillations can be initiated by changes in biophysical parameters and consider mechanisms that may enable the down-stream interpretation of dynamic gene expression. Our analysis illustrates how quantitative modelling can help unravel fundamental mechanisms of dynamic gene regulation.

## An epidemic model of the spread of mobile phone malware with quarantine and removal classes

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In March of 2018, about 500,000 desktop computers were infected with cryptocurrency mining malware in less than 24 hours. In addition to attacking desktop computers, malware also attacks laptops, tablets, mobile phones. That is, any device connected via the Internet, or a network is at risk of being attacked. In recent years, mobile phones have become extremely popular that places them as a big target of malware infections. In this presentation, the effectiveness of treatment for infected mobile devices is examined using compartmental modeling. Many studies have considered malware infections which also include treatment effectiveness. However, in this study we examine the treatment effectiveness of mobile devices based on the type of malware infections accrued (hostile or malicious malware). This model considers six classes of mobile devices based on their epidemiological status: susceptible, exposed, infected by hostile malware, infected by malicious malware, quarantined, and recovered. The basic reproductive number,  $\mathcal{R}_0$ , was identified to discover the threshold values for the dynamics of malware infections to become both prevalent or absent among mobile devices. In the analysis of the model, variables and parameters were defined to help observe the behavior of this system via graphical simulations. Because of the nature of malicious malware in phones, we found that an increase in our entrance and exit rates centered around that compartment outweigh any parameters in the hostile malicious malware compartment. To prevent infections of both types of malware, the best plan of action is to raise awareness of any third-party websites or to install an ideal anti-virus software to block any future attacks.

**Subdiscipline area:** Mathematical epidemiology

A growth based method for investigating the high shell shape variability in of the marine snail  
*Littorina saxatilis*

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The marine snail *Littorina saxatilis*, the rough periwinkle, is known for its high morphological variability related to local adaptations to different environments. In order to quantify and describe its shell shape variation we have developed a method for approximating a set of biologically meaningful parameters based on Raup's approach. This gives an intrinsic description based on logarithmic helicospirals which relate to the shells accretionary construction process, which can be used to understand how different aspect of shape relate to specific biological factors.

Our method has been applied to a large set of *L. saxatilis* shells collected across habitat transition zones on several separate islands on the Swedish west coast. We compared the distribution of values in the parameter space to describe the shape variation found within and between islands, habitats, and the sex of the snails. The results show that the largest part of the variation can be contributed to which environment the snails were collected from. In addition, we have found some differences between the islands, both in terms of the overall distribution in the parameter space, and whether or not there is any shape difference related to sex.

## A mathematical model of the effects of Amyloid beta on IP<sub>3</sub> signaling mechanisms.

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Alzheimer's disease is a devastating illness affecting over 40 million people worldwide. Intraneuronal rise of amyloid beta ( $A\beta$ ), has been linked to the pathogenesis of Alzheimer's disease by disrupting cytosolic  $Ca^{2+}$  homeostasis. We develop a mathematical model describing a proposed mechanism by which Phospholipase C (PLC) stimulation by  $A\beta$  triggers abnormal release of  $Ca^{2+}$  from the endoplasmic reticulum (ER) through activation of IP<sub>3</sub> receptor (IP<sub>3</sub>R)  $Ca^{2+}$  channels. We use experimental data to validate the model and quantify the effect of intracellular rise of  $A\beta$  on triggering PLC-mediated IP<sub>3</sub> over-production. Uncertainty quantification and partial rank correlation coefficients are used to better understand model solutions under various parameter regimes. Our analysis shows that the properties of the IP<sub>3</sub>R channel dynamics, and the upstream production of IP<sub>3</sub> can both influence solution patterns in the presence of  $A\beta$ . Model results illustrate and confirm the detrimental impact of  $A\beta$  on several crucial steps along normal functioning of IP<sub>3</sub> signaling pathways. The model also predicts that large  $Ca^{2+}$  flux can be diminished by altering G-protein activation and PLC-mediated IP<sub>3</sub> production potentially identifying therapeutic targets for AD.

Subdiscipline area: Mathematical Neuroscience (cellular mechanisms and biophysics)

## Modeling woundwood rib formation and fire scar closure in fire-scarred oaks

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Despite its tremendous importance to the creation and maintenance of habitat for wildlife and to effects on wood values for the timber industry, surprisingly little is known about the dynamics of the healing of wounds resulting from fire damage to trees. We present preliminary data on fire scar and woundwood morphology and growth which are used to motivate the development of a mathematical model of fire scar closure. Understanding the rate of scar closure is especially important in forest systems where prescribed burns are used in forest management as the interval between burns must allow for the closure of earlier fire scars to prevent increasing damage to the wood.

## Upscaling Individual Based Models to PDEs with Equation Learning

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Partial Differential Equations (PDEs) are often used to model the growth or movement of a group of individuals through space over time, e.g., the Fisher-KPP and Chemotaxis equations describe the movement of motile cells in the absence or presence of chemoattractant. New methods have recently been developed for learning partial differential equations (PDEs) from spatiotemporal data. These methods are capable of learning equations that describe complex systems without making assumptions about underlying mechanisms. However, whereas such PDEs describe individuals as a density over space that evolves with time, the biological systems they describe consist of individual agents, meaning that experimental data from these systems is most often discrete in nature and inherently noisy. We investigate a general approach to the learning of PDEs from spatiotemporal data generated by individual-based processes. We focus on data generated from discrete stochastic models, including random/biased walks and Cellular Automata (CA) models. We compare our findings from PDE learning with analytical methods that upscale individual-based models to PDEs in the continuum limit.

# Gene drive strategies of pest control and resistance management in agriculture

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Agricultural systems throughout the world are threatened by a number of pest species, including weeds, insects and pathogens. Controlling these pest populations is a significant challenge, hindered in particular by the ubiquitous occurrence of resistance to control agents such as chemical biocides. There is therefore a strong interest in novel control approaches to be added to the existing arsenal. Gene drives and associated genetic strategies have been proposed as potential novel control methods, particularly since the advent of CRISPR-Cas9 gene editing, that can be used to create theoretically efficient and versatile gene drives. There are however a number of uncertainties in the potential for these strategies to be transferred and work effectively in new target species and new, actively managed environments such as agrosystems. To address these uncertainties, we developed and present here a modelling framework designed to evaluate the outcome of gene drive strategies of pest control in agricultural systems. Within this stochastic, spatial, modular theoretical framework we focus on the ecological, biological and life history traits that are predicted to have the strongest impact on the success or failure of gene drive strategies, as well as their interaction with conventional control methods and associated resistance issues. As an example, we consider the potential application of gene drives to plants and weed control, and describe the challenges associated with both the technical feasibility of a gene drive as well as the population dynamics of such a drive in a plant population. We conclude by reviewing the spatial dynamics of a gene drive in our simulated populations, and the lessons that can be inferred for the potential future use of gene drives in an integrated toolkit for pest control and resistance management in agricultural systems.

## Modeling GnRH Neuronal Dynamics in Response to Kisspeptin Stimulation

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Pulsatile secretion of gonadotropin-releasing hormone (GnRH) from hypothalamic GnRH neurons tightly regulates the release of mammalian reproductive hormones. While key factors such as electrical activity and stimulation by kisspeptin have been extensively studied, the underlying mechanisms that regulate GnRH release are still not fully understood. Previously developed mathematical models studied hormonal release and electrical properties of GnRH neurons separately, but never integrated both components. Here we present a more complete biophysical model to investigate how electrical activity and hormonal release interact. The model consists of two components: an electrical submodel comprised of a modified Izhikevich formalism incorporating several key ionic currents to reproduce GnRH neuronal bursting behaviour, and a hormonal submodel that incorporates pulsatile kisspeptin stimulation and a GnRH autocrine feedback mechanism. Using the model, we examine the electrical activity of GnRH neurons and how kisspeptin effects GnRH pulsatility. The model reproduces the noise-driven bursting behaviour of GnRH neurons as well as the experimentally observed electrophysiological effects induced by GnRH and kisspeptin. Specifically, the model reveals that external application of GnRH causes a transient hyperpolarization followed by an increase in firing frequency, whereas administration of kisspeptin leads to long-lasting depolarization of the neuron. The model also shows that GnRH release follows a pulsatile profile similar to that observed experimentally and that kisspeptin and GnRH exhibit approximately 7-1 locking in their pulsatility. These results suggest that external kisspeptin stimulation with a period of 8 minutes drives the autocrine mechanism beyond a threshold to generate pronounced GnRH pulses every hour.

# Multi-level Approximate Bayesian Computation

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Mathematical models that describe real-world biophysical phenomena, such as those arising in population dynamics and ecology, frequently comprise intricate and unwieldy sets of equations that need to be parametrised. The versatility of Approximate Bayesian Computation (ABC) has rendered it a ubiquitous method for *inferring* suitable parameters from experimental data-sets [1, 2]. Despite its popularity, the considerable computational resources required to run an ABC algorithm has restricted the range of problems it can tackle. In this proposed contribution, we formulate a highly efficient ABC algorithm that uses machine learning methods to dynamically reduce the level of computational resources required for large-scale parameter inference.

In particular, we will set out a *multi-level* ABC inference method that is suitable for investigating the parameters of biophysical models described by a Master Equation [3]. Our approach is to generate sample paths of the model with varying time resolutions. We start by generating low-resolution sample paths that require only limited computational resources to construct. Then, a machine learning classifier recursively isolates subsets of the sample paths, and the temporal resolutions of the chosen sample paths are repeatedly increased. A posterior distribution is assembled by comparing the highest-resolution sample paths against experimental data-sets. The remaining sample paths are those that are unlikely to aid in parameter inference, and are thus promptly discarded.

The *multi-level* ABC algorithm is computationally efficient as it focusses on a small number of promising sample paths. The method's efficacy is demonstrated through two carefully chosen case studies.

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# Why be Temperate: On the Fitness Benefits of Lysis vs. Lysogeny<sup>1</sup>

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Bacterial viruses, i.e., ‘bacteriophage’, can infect and lyse their hosts, releasing new viral progeny. Yet temperate bacteriophage can also initiate lysogeny, i.e., a latent mode of infection, in which the viral genome is integrated into and replicated with the bacterial chromosome. Subsequently, the integrated viral genome, i.e., the ‘prophage’, can induce and restart the lytic pathway. The deferral of lysis – and the concomitant release of new virus particles – has led to a long-standing question: why be temperate? Here, we explore the dependency of viral fitness on infection mode and ecological context. By combining a cell-centric metric of fitness and a novel application of network loop analysis, we identify a universal form for viral fitness common to a spectrum of mechanistic models of phage-host dynamics. This universal form includes contributions to viral fitness from all possible infectious transmission paths that start and end with infected cells, rather than in terms of the production of virus particles. This universal form also reveals why lysogeny should be favored at low host abundances and why induction should occur rarely when integration is favored. Finally, we examine the robustness of viral strategies in an evolutionary framework, showing when temperate phage outperform lytic phage and when the enhanced fitness of lytic phage can, paradoxically, facilitate the subsequent invasion of less virulent strategies. Altogether, our results provide a principled framework for understanding the costs and benefits of being temperate.

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<sup>1</sup>SMB Subgroup: Population Dynamics, Ecology and Evolution  
<sup>2</sup>

# An interacting position jump model of glioblastoma growth

Gustav Lindwall\*  
Philip Gerlee†

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## Abstract

The brain tumour glioblastoma multiforme is characterized by diffuse and infiltrative growth into surrounding brain tissue. Efforts to model tumour growth using a mathematical framework have made great strides in the last few decades, and a wide array of mathematical methods have been applied to this emerging field. This includes phenomenological macroscopic models, data-driven statistical undertakings and physics-inspired bottom-up models utilizing stochastic processes. In this poster, we present two models mainly inspired by the theory of interacting particle systems. We let each individual cancer cell constitute a particle. We model cell division and death as Poisson processes with rates that depend on the local cell density. The cells are subject to a random isotropic motion modelled by mutually independent Wiener processes, but interact according to a pair potential which accounts for both volume exclusion and adhesion. The second model we consider incorporates phenotype switching between a resting and motile state. Here only resting cells are allowed to reproduce, a phenomenon observed both *in vitro* and *in vivo*. From the underlying stochastic models, transport equations for the cell density is derived.

These models are qualitatively compared to phase contrast microscopy images of cultivated cells. We make use of Partially Observed Markov Processes to determine the parameters of the individual based model. By considering a parabolic scaling we obtain partial differential equations for the cell density which describes the patterns of growth at the tumour scale. The natural next step after this study is to tackle the same problem using velocity based models, bringing further physical justification to the underlying dynamics and the ability to capture greater detail. The long term ambition of this research is to predict cancer progression in patients, and thus make better informed decisions on how to apply surgery and medical therapy.

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## B. Title and Abstract

### Development of an experiment-driven time-resolved model of response to radiation therapy

**Purpose:** To develop and validate a mechanism-based, mathematical model that characterizes the time-resolved response of glioma cells to radiation therapy *in vitro* by explicitly incorporating biological interactions with radiation including DNA repair and cell death pathways. The long-term goal is to use this model to make accurate predictions on the temporal evolution of glioma tumors receiving radiation therapy *in vivo*.

**Methods:** *in vitro*: 9L glioma cells are seeded at both low (500 cells) and high (10,000 cells) densities on a 96-well plate, and then irradiated at 0, 2, 4, 8, 10, 12, and 16 Gy at 1.5 Gy/min (130 keV, 5mA) using a Faxitron CellRad Irradiator (Faxitron, Arizona). Immediately after irradiation, phase-contrast images (for measuring total cells) and fluorescence images (for picking out dead cells) are acquired *via* the Incucyte Live-Cell imaging system (Essen Bioscience, Michigan) every 3 hours for 150 hours. The images are used to estimate live cell confluence over time. DNA damage is estimated using gamma-H2AX immunofluorescence as measured by flow cytometry.

*in silico*: A our current model describes the temporal evolution of tumor growth through ordinary differential equation (please see Eqs. [1] and [2] below) consisting of a logistic proliferation term, the Allee effect term, and a death term:

$$\frac{dN}{dt} = k_p \overbrace{N \left(1 - \frac{N}{\theta}\right)}^{\text{Logistic}} \overbrace{\left(\frac{N}{\theta} + A\right)}^{\text{Allee}} - k_d N \quad [1]$$

$$k_d = \overbrace{k_{d,f} \cdot f_{dsb}(t)}^{\text{Early death}} + \overbrace{k_{d,a} \cdot r \cdot (t - T)^+ \cdot e^{1-r(t-T)^+}}^{\text{Late death}}, \quad [2]$$

where  $N$  is the cell confluency,  $k_p$  is the proliferation rate,  $A$  characterizes Allee effect,  $\theta$  is the carrying capacity,  $k_{d,f}$  is the fast death rate,  $k_{d,a}$  is the accumulation death rate,  $r$  is a parameter related to how fast radiation effect decays,  $f_{dsb}(t)$  is the fraction of unrepaired double strand breaks (measured from flow cytometry), and  $T$  is the time delay for accumulation death. The death term accounts for both early cell death (due to extensive unrepairable DNA damage) and late death which occurs after one or more cell divisions leading to (for example) mitotic catastrophe. The model was then fit to the *in vitro* data using the Levenberg–Marquardt algorithm to estimate  $k_{d,f}$  and  $k_{d,a}$ ,  $r$ , and  $T$ .

**Results:** The early death rate is 0.0085 hr<sup>-1</sup> (for 2 Gy) and 0.06 hr<sup>-1</sup>(for 16 Gy); however, this effect plays a small role as double strand breaks are repaired quickly (>80% repaired within 24 hours for doses up to 16 Gy). As the dose increases, the death rate  $k_{d,a}$  gradually increases from 0.021 hrs<sup>-1</sup> (for 2 Gy) to 0.044 hrs<sup>-1</sup> (for 16 Gy). The time delay  $T$  for accumulation death decreases from 63 hrs (for 2 Gy) to 18 hrs (for 16 Gy) indicating a stronger response of cells to radiation.

**Conclusion:** Preliminary results indicates model parameters depend on the dose cells receive in a monotonic fashion. Current modeling efforts demonstrate promising steps towards realizing a time-resolved model of radiation response, which could, eventually, be used to predict, and optimize, tumor response *in vivo*.

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## C. Mathematical Oncology

## A polynomial metric on rooted binary tree shapes

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In this talk, we will define a polynomial and show that the polynomial characterizes all rooted binary tree shapes, that is, two unlabeled rooted binary trees are isomorphic if and only if their corresponding polynomials are identical. Metrics on rooted binary tree shapes can be induced from this characterizing polynomial. We will show that these metrics can distinguish random tree shapes generated by different models as well as phylogenetic trees of seasonal and tropical influenza.

## An evolutionary model of within-host mutation and between-host pathogen transmission

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The effect of within-host dynamics on the transmission and evolution of bacterial pathogens has attracted attention in the literature in recent years. Understanding the mechanisms that influence the appearance of mutants and the effect of selection on mutant frequencies within hosts is important for gaining insight into how new strains arise at a host population level. These insights may add to our understanding of, for example, the evolution of resistance. The emergence of mutant strains suggests potential for increases in diversity, however, despite the diversity revealed through the genetic analysis of pathogens, genetic variation appears to be lower between hosts than within hosts. This indicates two dynamic scales at which strain frequency can be influenced. Mutant strains may be prevalent due to mutation and the immediate selective effects of these mutations within hosts, but may not be easily transmitted between hosts. The different mechanisms acting at these two scales remains to be clarified. We develop a model of within-host dynamics, where mutations arise and are subject to positive or negative selection and we investigate the effect of these dynamics nested within an epidemiological model. We consider the effect of selection on the overall population transmission dynamics between hosts by assuming that mutations can act in one of two ways: mutants can escape host immunity, or they can have altered growth rates compared to the wild-type. In both of these models, it is clear that the bottleneck that occurs at disease transmission acts as a strong brake on selection at the population level. By developing a model of mutation accumulation and selection in acute infections within an agent-based SEIR model, we compare population diversity between these two pathways of selection.

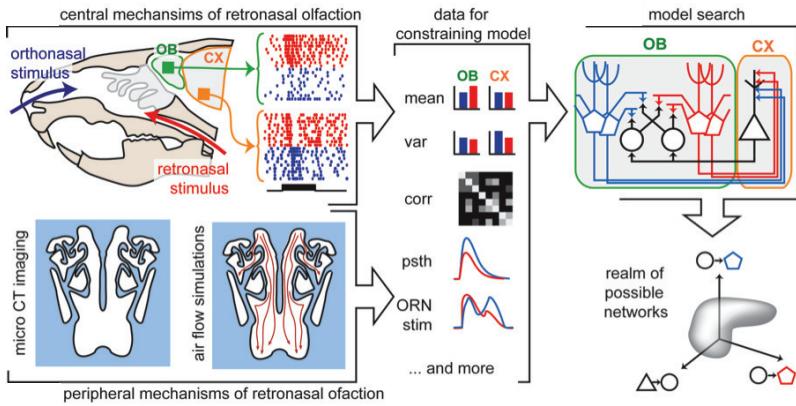


Figure 1: Simultaneous dual array recordings of the olfactory bulb (**OB**) and anterior piriform cortex (**CX**) lead to many constraints with different regions and states (spontaneous vs. evoked). The realm of possible models (parameters) that have spiking activity consistent with the data is narrow.

## Spike statistics during olfactory stimulation via orthonasal and retronasal inhalation

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Electrophysiological experiments are fundamental in advancing our understanding of neural processing of information. Currently, however, experiments are limited in revealing circuit details; for example, accessing dynamics of connection strengths amongst different cell types and across multiple brain regions is currently elusive. I will present some recent work detailing how theoretical and computational methods can be useful in these efforts. We have developed a data-driven framework to predict relative connection strengths in multilayered populations, and applied it to the rodent olfactory system under orthonasal (normal breathing) and retronasal (odors originating from the back of nasal cavity) inhalation. Our modeling work provides novel experimental predictions about how the spike train statistics change with pharmacological manipulations. This work can serve as a guide to further investigations into the relationships of various neural attributes within and across different regions during sensory processing.

**C. Subdiscipline area:** Mathematical Neuroscience

## Modelling approaches to describe tumour-immune competition and tumour development

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The ability of the human immune system to detect and remove cancer cells is exploited in the development of immunotherapy techniques. However, further understanding of the key mechanisms involved is required, this can be achieved through the use of computational and mathematical models. We have developed individual-based models of tumour-immune competition by considering the spatio-temporal interactions between dendritic cells, cytotoxic T cells and a solid tumour. Among other key mechanisms, we have explicitly considered the immune recognition of evolving tumour antigens and the experimentally observed migration patterns of immune cells in the tumour micro-environment. Computational simulations of our models clarify the conditions for the onset of a successful immune action against cancer cells and may suggest possible targets to improve the efficacy of immunotherapy. However, discrete approaches to modelling can be limited in their amenability to different mathematical analysis techniques which are better suited to continuum models. To overcome this we aim to derive the continuum version of our described individual-based models. Due to the complexity of the biological mechanisms included, we first considered a simpler biological situation of (tumour) cell invasion. We developed an individual-based model describing the spatial dynamics of multicellular systems whereby cells undergo pressure-driven movement and pressure-dependent proliferation. From this, we formally derived nonlinear partial differential equations that are commonly used to model the spatial dynamics of growing cell populations. Through systematic comparison between both models, we demonstrated that the results of computational simulations of the individual-based model faithfully mirror the qualitative and quantitative properties of the solutions to the corresponding partial differential equations. This method could be adapted to more complex individual-based models, such as those we have developed to describe tumour-immune competition.

## Double-wave Reentry in Excitable Media

Eric N Cytrynbaum<sup>1</sup>, **Vincent MacKay (presenter)**<sup>2</sup>, Olivier Nahman-Lévesque<sup>3</sup>, Matthew Dobbs<sup>4</sup>, Gil Bub<sup>5</sup>, Alvin Shrier<sup>6</sup>, and Leon Glass<sup>7</sup>

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A monolayer of chick embryo cardiac cells grown in an annular geometry supports two simultaneous reentrant excitation waves that circulate as a doublet. We propose a mechanism that can lead to such behavior. The dispersion relationship gives the instantaneous velocity of a wave as a function of the time since the passage of the previous wave at a given point in space. Non-monotonic dispersion relationships will lead to situations in which various spacings between circulating waves are possible. In cardiology, the situation in which two waves travel in an anatomically defined circuit is referred to as double-wave reentry. Since double-wave reentry may arise as a consequence of pacing during cardiac arrhythmias, understanding the dynamic features of double-wave reentry may be helpful in understanding the physiological properties of cardiac tissue and in the design of therapy. Neural tissue also being an excitable medium, this research relied on previous literature in neuroscience, which has approached questions in wave propagation using dispersion relationships in a similar way. This suggests that our findings might be transferable to the context of nonlinear wave dynamic problems in the neural system.

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## Phase Reduction and Synchronization Through Environmental Noise in Stochastic Biochemical Oscillations

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Subject Areas: Mathematical Neuroscience, Developmental Biology

A common method for analyzing the effects of molecular noise in biochemical reaction networks is to approximate the underlying chemical master equation by a Fokker-Planck equation, and to study the statistics of the associated chemical Langevin equation. This so-called diffusion approximation involves performing a perturbation expansion with respect to a small dimensionless parameter  $\epsilon = \Omega^{-1}$ , where  $\Omega$  characterizes the system size. For example,  $\Omega$  could be the mean number of proteins produced by a gene regulatory network. In the deterministic limit  $\Omega \rightarrow \infty$ , the chemical reaction network evolves according to a system of ordinary differential equations based on classical mass action kinetics. In this talk I develop a phase reduction method for chemical reaction networks that support a stable limit cycle in the deterministic limit. We present a variational principle for the phase reduction, yielding an exact analytic expression for the resulting phase dynamics, and demonstrate that this decomposition is accurate over timescales that are exponential in the system size  $\Omega$ . This contrasts with the phase equation obtained under the diffusion approximation, which is only accurate up to times  $\Omega$ . In particular, we show that for a constant  $C$ , the probability that the system leaves an  $O(\zeta)$  neighborhood of the limit cycle before time  $T$  scales as  $T \exp(-C\Omega b\zeta)$ , where  $b$  is the rate of attraction to the limit cycle. We illustrate our analysis using several examples, including the Morris-Lecar oscillator in neuroscience.

Next, we look at synchronization through common environmental noise in gene regulatory oscillations. It is common in cell biology to distinguish between extrinsic noise (i.e. environmental, felt by many cells) and intrinsic (i.e. irregularities within the cell due to low copy numbers, inhomogeneities in local cellular topology). We demonstrate that if there is some correlation between the extrinsic noise afferent on two different cellular oscillations, then one should expect some synchronization in the phases of the oscillators over time. These results are applied to an oscillation in gene regulatory networks that results from a combination of bursting with delayed inhibition.

## On the concept of temperature in the process of aging and AML development

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Aging is an inevitable and universal process which involves multiple complex changes at molecular and cellular levels that lead to decline in physiologic reserve capacity across virtually all organ systems. The presence of diseases and accumulation of cellular damage aggravates the hallmarks of aging and lead to acceleration in the process of aging. It is therefore crucial not only to identify and to investigate these processes in a statistical sense, but also to study how they evolve in time.

Genomic data collected over time offers a promising opportunity to predicting disease evolution in relation to the rate of aging. However, current approaches to the analysis of time-series genomic data is predominantly statistical in nature and does not provide a fundamental understanding of the system. Because the methylation state of the genome is recognized as an important biomarker which can be used to define the biological age, here we propose a mathematical model which associate a methylation profile a quantity analogous to a thermodynamic temperature  $T$ . The foundation of our approach is the Ising model of magnetism. We study the correlation function associated with a sequence of methylated or unmethylated sites in the genome with data collected from the peripheral blood of a mouse model of acute myeloid leukemia (AML).

With this approach, the process of aging or disease development is modeled as a time evolution of a thermodynamic process characterized by a well-defined thermodynamic temperature. Here we will present and discuss the connection between temperature and entropy, allowing for a characterization of the process of disease development in the context of the rate of aging as measured through changes in the epigenetic state of the genome.

## MODELING THE STIMULATORY NETWORK IN NATURAL KILLER CELLS

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### Abstract

Natural killer (NK) cells are innate immune cells that eliminate diseased cells by releasing cytotoxic chemicals upon activation. Excitingly, NK cell-based immunotherapies are shown to be effective against hematological cancers; however, similar success against solid tumors still remains a challenge. A better understanding of the pathways regulating NK cell activation can provide insight into strategies for optimizing these therapies. We constructed a mechanistic model of the CD16, 2B4 and NKG2D stimulatory pathways. The model was fit to published data and validated with a separate dataset. Baseline model predictions demonstrate the qualitative similarities between CD16 and NKG2D stimulation; they activate the downstream species to a greater degree and at a faster rate when compared to 2B4. Contrastingly, 2B4 stimulation activates the signaling species over a longer time interval. Interestingly, the model predicts that 2B4 co-stimulation with either CD16 or NKG2D produces optimum activation of the Src family kinases (SFK), which are the species responsible for initiating signal transduction. *In silico* perturbations of the signaling networks highlight how phosphatases control signal transduction. Moreover, inhibiting the activation of the phosphatases is predicted to significantly enhance species activation. In summary, the model predicts: (1) qualitative differences between the pathways, (2) co-stimulation of qualitatively different pathways induces optimal activation of the signal transducer (pSFK) and (3) inhibiting the activation of the inhibitor significantly increases the rate and magnitude of species activation. This detailed mechanistic insight can help design NK cell-based immunotherapies.

# Can One Enzyme Isoform Compensate for Knockout of Another in Cellular Rhythmogenesis?

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\* Presenter

Insulin is released in a pulsatile manner by the pancreatic  $\beta$ -cells, as a result of electrical impulses generated in bursts when glucose concentration in the blood is in a stimulatory range. One form of bursting, compound bursting, has been hypothesized to be driven by oscillations in glycolysis. The oscillations in glycolysis are regulated by the allosteric enzyme phosphofructokinase (PFK), which converts the substrate fructose 6-phosphate (F6P) into fructose-1,6-bisphosphate (FBP). More precisely, the oscillations result from the positive feedback of FBP onto PFK. At least two different isoforms of PFK are expressed in pancreatic  $\beta$ -cells: the muscle isoform PFK-M and the brain isoform PFK-C. It has been shown that most PFK activity in  $\beta$ -cells is mediated by the PFK-M isoform, and biochemical studies complemented by mathematical modeling have shown that this isoform is capable of generating oscillations through positive feedback and substrate depletion. It has therefore come as a surprise that compound bursting oscillations persist in  $\beta$ -cells in which the PFK-M isoform has been genetically knocked out. In this modeling study, we demonstrate how the PFK-C isoform, which is generally thought to not have rhythmogenic properties, can nonetheless compensate for PFK-M knockout, without the need for upregulation of the compensating enzyme isoform protein levels.

## When activators become inhibitors: emergent spatial patterns in meta-ecosystems

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Ecosystems can be characterized by hierarchical stocks and flows of matter. Higher trophic levels are typically composed of a few large individuals that move rapidly over large distances while lower trophic levels contain many small individuals that move slowly over short distances. Such structuring can help explain the spatial patterns of ecosystems based on classical activator-inhibitor systems. The lower trophic levels can act as activators due to short-range positive feedbacks while higher trophic levels act as inhibitors that cause diffusive negative feedbacks. These feedbacks then create stable spatial patterns with areas of low and high density for lower trophic levels. It remains an open question whether the presence of multiple activator species at the same trophic level. In addition, in a meta-ecosystem, there may be effects from feedbacks through nutrient recycling within ecosystems and nutrient movement between ecosystems. In this talk, we present a meta-ecosystem model with one limiting nutrient-two primary producers-one herbivore that examines these questions. Our results show that high levels of diffusion by the non-dominant primary producer can lead to stable spatial patterning without any substantial herbivore movement. We suggest that through apparent competition, this primary producer acts like an inhibitor for the other primary producer. However, this effect is modulated by the presence of nutrient movement. Therefore, the net effect between ecosystem compartments is required to fully understand the conditions for spatial pattern formation in meta-ecosystems.

## Applications of Multiscale Simulation Algorithms to Angiogenesis Models

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Angiogenesis is the process by which new blood vessels are created from existing vascular networks. It occurs naturally as part of wound healing and embryonic development; however in the context of cancer biology tumors can stimulate angiogenesis in order to construct a vascular network that provides nutrients for continued growth of the tumor and a route for metastasis. Angiogenesis begins with the secretion of tumor angiogenic factors (TAFs) such as VEGF, which activate endothelial tip cells that line the walls of existing capillaries. The tip cells then move via diffusion and chemotaxis towards TAF sources, are produced via branching events, and form closed circulatory loops via anastomosis. The new vascular networks are created by endothelial cells that follow the paths of these tip cells; the complete process is commonly referred to as a snail-trail. Mathematical descriptions of the snail-trail have typically considered tip and endothelial cells at only the macroscopic, mesoscopic, or microscopic level, depending on the amount of detail desired. This may lead to computational intractability in the case of microscopic models or to a loss of information about the vascular network formed in the mesoscopic and macroscopic cases.

In recent years, researchers have developed multiscale computational algorithms to accelerate the solution of small-scale models for a variable of interest. Such methods partition a spatial domain into regions that either contain the fine-level stochastic model or, depending on the validity of coarse-level approximations, its larger scale (possibly deterministic) equivalent. These techniques have been developed for macroscopic-microscopic (the Auxiliary Region Method), macroscopic-mesoscopic, and mesoscopic-microscopic (the Adaptive Two Regime Method) simulation; each algorithm can provide the same level of detail as a full stochastic model (albeit in a portion of the full domain) whilst generating solutions in a much faster time frame. Multiscale computational methods applied to angiogenesis models have the potential to investigate the role of individual tip and endothelial cells at a local level while providing computational tractability via coarser-level descriptions elsewhere in the domain.

In this presentation, we apply multiscale algorithms to simulate and analyze the process of tumor-induced angiogenesis. We compare and contrast results both qualitatively and quantitatively using different algorithms, in order to determine efficient and accurate methods for computing the multiscale behavior of angiogenesis over the full domain.

## Growth On Multiple Limiting Essential Resources In A Self-Cycling Fermentor

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\* Presenting author

We introduce a model for the growth of a single microorganism in a self-cycling fermentor where an arbitrary number of resources are limiting, and impulses are triggered when the first substrate reaches a limiting concentration. The resource uptake is modeled by Liebig's law of the minimum, and individual response functions are assumed to be monotone increasing. We consider the operation of the reactor to be successful if it cycles indefinitely, and derive sufficient conditions for this to be the case. We prove that when the reactor is successful, solutions converge to a unique periodic solution. We also show that, unlike in the single resource case, it is possible for the system to undergo many impulses before failing, and illustrate this with some numerical examples.

## Weaving a Tangled Web: Neurons and Networks

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Dynamical processes on networks are relevant to numerous systems ranging from communications, infectious diseases, social interactions and the central nervous system. Neuronal networks are vastly complex with numbers of neurons in the human brain on order  $10^{11}$  and numbers of connections between them are even more staggering. We are investigating statistical properties of these network systems such as correlations of input and output connections for an individual neuron, and assortativities or propensities of linkages between, say, high-input and low-output neurons. Additional concerns such as the unidirectional aspect of neuronal information flow, addition or removal of auto-stimulation or multiple linkages between two neurons further complicate the process. We present various methods of assembly for these networks, and some of the techniques for optimising and reducing the overall computational difficulties encountered enroute to our investigations of emergent behaviours in networks and implications for physiological systems.

## Modeling the Influence of Social Interactions on Physical Fitness

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There are increasing efforts to promote healthy physical fitness attitudes and behaviors in larger populations through community interventions. The purpose of these interventions is to create wide-spread, positive behavior changes throughout the community. A critical aspect of community interventions involves drawing upon the social environment that supports and promotes the desired behavior. We use a differential model (based on the ideas of Kermack and McKendrick for infectious disease modeling) to determine whether social environment influences exercise habits among sedentary individuals when they become exposed to active individuals. We use the unique data available at the United States Military Academy to estimate parameters and thresholds required to draw and sustain individuals toward improved physical activity habits. Our goal is to identify the optimal social environment that draws individuals towards improved physical fitness.

## Sensitivity to larval settlement cues affects marine population viability

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Over 70% of marine species have a planktonic larval stage. Dispersing largely as passive floaters, only a small fraction of these larvae reach suitable habitats before the end of their effective lifetimes. Larval experience informs fitness in subsequent life stages, with late-settling larvae being less likely to survive to reproduction. Thus, the age distribution of settling larvae directly impacts population viability, and it is essential that larvae can promptly settle in response to indicators of habitat quality.

We investigate the response of the larval settler age distribution to the intensity and physical layout of indicators of habitat quality by modeling the cross-shore position of an individual larva as a stochastic diffusion. Preliminary results show that weakened responsiveness to these cues increases the proportion of old larvae settling into the population. Furthermore, we found that given two coastal habitat patches of unequal attractiveness, the more attractive patch tends to harbor a younger population of settlers. Experiments have shown that increased oceanic CO<sub>2</sub> content can impair larvae's ability to distinguish habitat quality—even causing rejection of good sites in favor of poor or non-existent ones. Thus, our results highlight an unexpected potential consequence of climate change and emphasize the need for a deeper understanding of the potential for larval habitat selection mechanisms to evolve in near-future conditions.

## Assessing the impact of empirical contact patterns on disease dynamics within an equine population

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Disease transmission models often assume homogenous mixing which is not always representative of the population-level mixing patterns and can result in an over- or underestimation of the disease dynamics within the population of interest. Recent technological advances have enabled the collection of detailed contact pattern data, facilitating the incorporation of more accurate mixing patterns in the model. However, the optimal method of integrating the data in the model is unclear. The purpose of this work was to explore the impact of empirical contact pattern data on disease dynamics within a population.

A stochastic SEIR model was used to simulate disease spread within equine populations using equine influenza as a case study. Three intervention scenarios were modeled: 1) no intervention, 2) the singular use of vaccination or isolation, and 3) a combined vaccination and isolation strategy. The model contact rate was informed with both empirical and theoretical contact networks. Each simulation was run using both weighted and unweighted networks. The model outcomes were compared in order to assess the influence of the different types of contact pattern data on the disease dynamics within the population.

The incidence curves generated with the empirical contact pattern data were bimodal while those generated with the theoretical networks were unimodal. The incorporation of theoretical networks in the model resulted in similar incidence curves, regardless of whether the networks were weighted or unweighted. In contrast, the incidence curves for the models informed with the unweighted, empirical networks were similar in shape, epidemic peak height (30.8-46.4%), and epidemic duration (5-8 days). Alternately, the weighted empirical networks resulted in a larger range for both the epidemic peak height (5-25%) and the epidemic duration (8-15 days). Lastly, the incorporation of a combined vaccination and isolation program in the model resulted in a non-linear trend in cumulative incidence at high levels of isolation for the unweighted networks. This trend was not observed in the weighted networks. This study emphasizes the effect of different contact networks on disease dynamics within a population. Given the results, empirical contact pattern data should be used to inform models for populations that are unlikely to exhibit homogenous mixing.

## Mathematical modeling of the role of macrophages in lung inflammation

**Sarah B. Minucci**<sup>a\*</sup>, Rebecca L. Heise<sup>b</sup>, Michael S. Valentine<sup>c</sup>, Franck Kamga Gninze<sup>d</sup>, and Angela M. Reynolds<sup>e</sup>

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Mechanical ventilation is used to provide support to the lungs for patients with severe breathing issues, but as the air is pushed into the alveolar space it can trigger an immune response which leads to ventilator-induced lung injury (VILI). Macrophages are immune cells essential to the response of this injury, and imbalances in macrophage levels cause serious complications for the patient. The spectrum of macrophage activation provides insight into the roles that each phenotype plays in the immune response. We develop a system of ordinary differential equations (ODEs) to model the immune response to VILI, including two compartments: the bloodstream and the site of inflammation at the epithelial barrier. We also include two types of macrophages on each end of the activation spectrum: pro-inflammatory M1 and anti-inflammatory M2. To our knowledge, this model is the first to account for various states of the epithelial cells' (healthy, damaged, and dead) response to stretch-induced damage. We use dynamical system approaches and sampling of parameter space to analyze the VILI immune response and understand what mechanisms drive different responses. Fitting early time-point data generates varied dynamics, giving rise to multiple outcomes corresponding to health, moderate damage, or severe damage. These modeling efforts will help to guide design of future experiments, predict patient outcomes more effectively, and provide recommendations for treatment.

## Extracting positions of sheep from drone footage for model comparisons

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The spectrum of biological systems exhibiting group motion is wide and includes cases such as bacterial colonies, migrating locusts, schools of fish, flocks of birds, groups of mammals (including humans) and so on. Various agent-based models have been proposed [1],[2],[3] attempting to capture this motion. These include Vicsek's model [1] of self-propelled particles, which captures inter-flock interactions, and more recently a minimal model involving predator-prey interactions [3]. However, these models are relatively unconstrained due to a paucity of high-quality observational data of co-operative motion. Our study, based on observations of sheep herds is a step in this direction. The work is not only of academic interest, recent technological advances have lead to an increase of the commercial applications of accurate identification and movement of livestock.

Here we demonstrate an algorithm developed to accurately identify the number of and location of sheep in 3 dimensions (2D space + time). We use computer vision methods including a combination of blurs, filters and thresholds from the OpenCV package. The videos of herding were captured from above using a DJI Phantom 3 drone equipped with a video camera, filmed at up to 2.7K ( $2704 \times 1520$  pixels) resolution at 24 f.p.s.

We demonstrate the accuracy of the developed algorithm and discuss current work to both constrain and extend the models of collective motion.

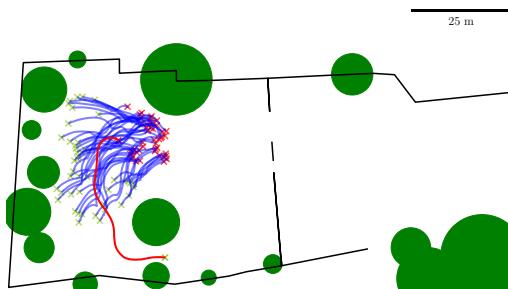


Figure 1: Resulting trajectories of 45 sheep being herded by a quad bike. Blue trajectories show the tracked sheep, and the red shows the path of the quad bike.

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## B. Title and Abstract

Understanding rabies persistence in low density fox populations

Arctic Fox (*Vulpes lagopus*) and its tundra habitat is a unique system for the study of rabies virus epidemics. Contrary to theoretical calculations that report a critical density ( $K_T$ ) of approximately 1 fox/km<sup>2</sup> for rabies endemicity, arctic rabies persists at densities well below this. The calculation of  $K_T = 1$  fox/km<sup>2</sup> assumes a uniform fox density across the landscape and unrestricted mixing between susceptible and infected foxes. We hypothesize that spatial heterogeneity arising from resource distribution or social structure may result in regions where rabies is endemic, even though average fox density at the landscape-level is below  $K_T$ . We use mathematical models to identify the conditions that allow rabies to persist in a metapopulation structure, and seek to understand how the partitioning of densities into patches with local infection dynamics can support rabies, even when landscape-level averages fall below  $K_T$ . This study shows that source-sink disease dynamics and moderate levels of patch connectivity allow for rabies endemicity in low density patches.

## C. Subdiscipline Area

Mathematical Epidemiology

## Modelling the evolution of flowering onset in perennial plants

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A plant initiates flowering at a certain time during the growing season. Flowering early (and hence longer) could increase the prospect of pollination, but typically reduces vegetative growth and yields fewer/smaller flowers. Flowering late (and hence shorter) guarantees more/bigger flowers but carries the obvious risk of insufficient pollination. This trade-off could become particularly important in a changing climate, where the length of the growing season is expected to change, and in the context of range expansion, where plants may be maladapted to local conditions.

We present a novel deterministic hybrid integrodifferential model where we represent the growing season in continuous time and the time between seasons as a discrete map. We explicitly consider flowering onset as a variable in our model and look at the density of flowers with respect to this trait. We analyze the evolution of flowering onset in our model from two different viewpoints: (1) by mutual invasion analysis in the sense of adaptive dynamics; and (2) by reduction to a model for the mean trait value and total population density in the spirit of quantitative genetics. In each case we find an intermediate optimal flowering time for our model.

## A Structured Population Model for Lipid Accumulation in Macrophages

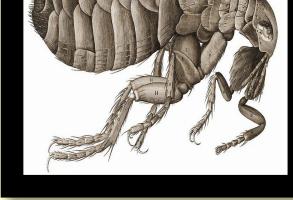
Mary R Myerscough<sup>a</sup>, Hugh Z Ford<sup>b</sup>, and Helen M Byrne<sup>c</sup>

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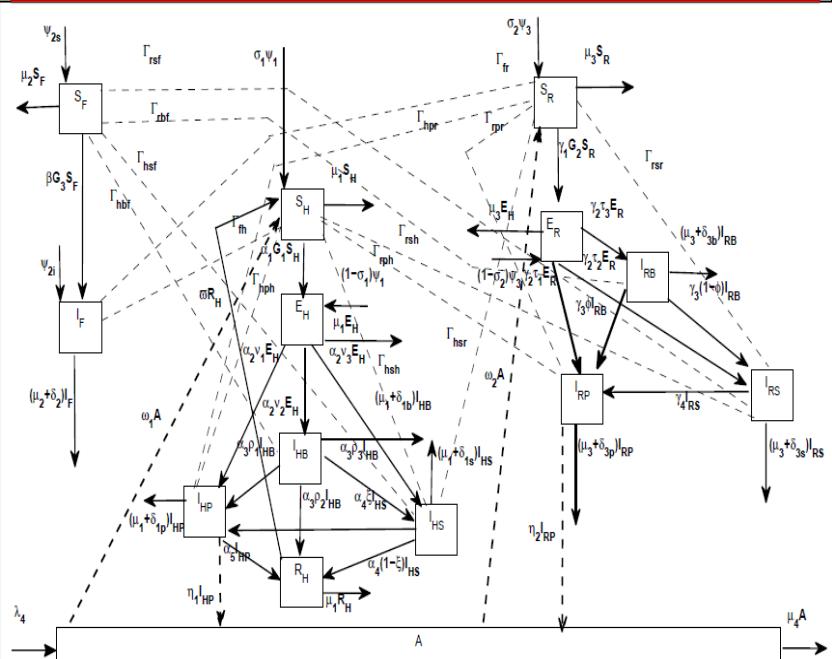
Macrophages are typical cells that are found in atherosclerotic plaques and may contribute either to plaque growth or to plaque resolution. Macrophages accumulate internalised lipids, such as cholesterol, both through ingesting modified low density lipoprotein particles (LDL) and through ingesting other macrophages that have undergone apoptosis. In this way macrophages may accumulate so much internalised lipid that they take on a foamy appearance under the microscope and are known as foam cells. We present an advective PDE model for the populations of macrophages and apoptotic cells, structured by their internalised lipid content. We find steady state solutions analytically and use this model to explore the factors that contribute to plaque progression and regression. The model shows impressive agreement with *in vitro* experiments in the case when lipid accumulation is due to ingestion of apoptotic cells only.



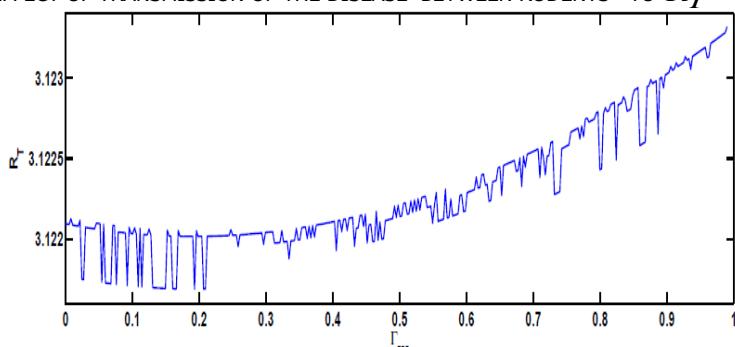
## ABSTRACT

A mathematical model to study the effect of seasonal weather variation on the dynamics of plague disease is developed and analyzed. Using ordinary differential equations, we formulate a model for the dynamics of plague disease in four settings namely: Human beings, Rodents, Fleas and Pathogens in the environment. We found that the variation in number of plague disease cases mainly depend on: the transmission rate of infection from one individual to another; the incubation period of an individual and the time that an individual remains infectious. The analysis further reveals that the effects posed by seasonal weather variation depends on the extent to which the weather variation favours the transmission of plague disease (amplitude of seasonality) and the duration that it remains in favour of the increase or decrease of the rate of disease transmission and spread. Therefore the control strategies should target these factors and parameters that according to our results stated above have shown to have a significant effect on the dynamics of plague disease. We thus recommend the provision of education on plague disease infection, transmission and spread to raise people's awareness, continuous monitoring of factors that may lead to plague outbreak, easy access of plague disease treatment for all and the strong collaboration with neighboring countries on health related issues.

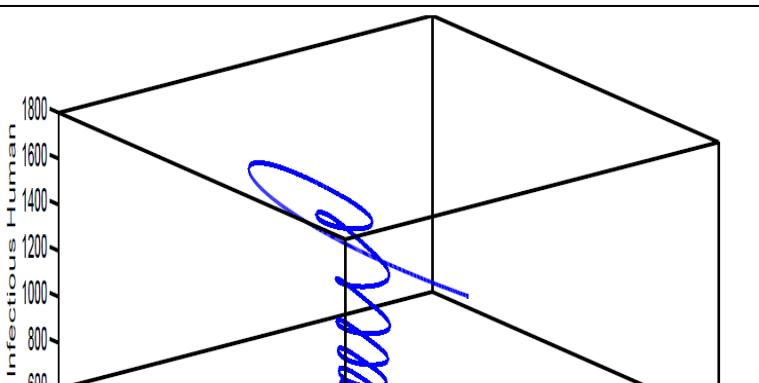
## **COMPARTMENTAL DIAGRAM**



## EFFECT OF TRANSMISSION OF THE DISEASE BETWEEN RODENTS TO $R_T$



## DYNAMICS IN HUMAN POPULATION



## **INTRODUCTION**

Plague is a zoonotic infection and serious bacterial disease that can be deadly. The disease is caused by bacteria called *Yersinia pestis* a pleomorphic, gram-negative non-spore-forming coccobacillus that is more accurately classified as a subspecies of *Y pseudotuberculosis*, named after the French-Swiss bacteriologist Alexandre Yersin. Different studies have been carried out with the aim of understanding the plague disease in terms of the factors that led to the occurrence of the disease and its dynamics. The aim is to develop proper ways of controlling and overcoming the epidemic when it occurs. However, most of them did not consider the enzootic cycles in non-human hosts, and for those that did they assumed non-human hosts as being incapable of transmitting plague disease. Most studies consider non-human hosts as a reservoir of the *Yersinia pestis* that will be taken to human beings through a vector flea. Moreover, although most of the parameters that dictate the transmission and spread of plague disease are affected by seasonal weather variation, available studies have not exhaustively analyzed mathematically the effect of seasonal weather variation in the dynamics of plague disease.

In this study, we explore the mathematical modeling of the dynamics of the plague infections. We consider human host, non-human host and environment as plague disease transmission agents. We consider possible ways/modes of transmission of plague disease which are mainly direct physical contact, vector borne transmission, airborne transmission and indirect contact with respect to the features of the form of plague disease one has. We also extend our study to cover the effect of the parameters that may be affected by seasonal weather variation on the dynamics of the plague disease. We then develop a generic plague model (the model that combine all three forms of plague disease) that considers all factors that enable plague disease transmission including that of seasonal weather variation in order to extensively understand the dynamic of plague disease. We analyze the model to explain the conditions for existence, persistent and extinction of the disease, the stability and existence of positive periodic solution, disease-free equilibrium and the system's behavior through numerical simulation.

## **GENERAL OBJECTIVE**

The main objective of this study was to develop a fully bodied mathematical models to study the dynamics of plague disease, and asses the effect of seasonal weather variations on its transmission.

## **STAGES OF ANALYSIS**

1. To formulate and analyze basic mathematical models for bubonic plague dynamics and explore its behavior using numerical simulations
  2. To formulate and analyze basic mathematical models for pneumonic plague dynamics and explore its behavior using numerical simulations.
  3. To formulate and analyze the basic combined deterministic mathematical model for the dynamics of plague disease that will include all three forms of plague disease and all major ways/modes of plague disease transmission
  4. To formulate and analyze the plague disease model incorporating with parameters that are affected by seasonal weather variation.

## MODEL EQUATION FOR HUMAN BEINGS

$$\begin{aligned}\frac{dS_H}{dt} &= \psi_1 + \varpi R_H - \alpha_1 G_1(t) S_H - \mu_1 S_H, \\ \frac{dE_H}{dt} &= \alpha_1 G_1(t) S_H - \alpha_2 E_H - \mu_1 E_H, \\ \frac{dI_{HB}}{dt} &= \alpha_2 \nu_2 E_H - \alpha_3 I_{HB} - (\mu_1 + \delta_{1b}) I_{HB}, \\ \frac{dI_{HS}}{dt} &= \alpha_3 \rho_3 I_{HB} + \alpha_2 \nu_3 E_H - \alpha_4 I_{HS} - (\mu_1 + \delta_{1s}) I_{HS}, \\ \frac{dI_{HP}}{dt} &= \alpha_2 \nu_1 E_H + \alpha_3 \rho_1 I_{HB} + \alpha_4 \xi I_{HS} - \alpha_5 I_{HP} - (\mu_1 + \delta_{1p}) I_{HP}, \\ \frac{dR_H}{dt} &= \alpha_3 \rho_2 I_{HB} + \alpha_4 (1 - \xi) I_{HS} + \alpha_5 I_{HP} - \varpi R_H - \mu_1 R_H.\end{aligned}$$

## PLAQUE INTRODUCTION AND SPREAD IN TANZANIA



# The minimal model of Hahn for the Calvin cycle

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**Abstract:** There are many models of the Calvin cycle in the literature. Due to their big sizes, models were mostly numerically investigated or using reduction techniques. We investigate a simple two dimensional model of the Calvin cycle proposed by B.D. Hahn in favor of getting the most detailed insights. In a variant of the model not including photorespiration, it is shown that there exists exactly one positive solution which is unstable. For generic initial data, concentrations tend to infinity and were later tracked using Poincaré compactification. When photorespiration is included and for a suitable choice of parameters, bistability is proved. For generic initial data either the solution tends to the stable steady state at late times or all concentrations tend to zero at late times. Rigorous mathematical proofs emphasize the idea that photorespiration stabilizes the operation of the Calvin cycle, although at the price of reducing the efficiency of the carboxylation reaction. This would suggest another considering of photorespiration not as a wasteful competitive process to carboxylation, but as stabilizer which prevents overproduction in the cycle. Additionally we reduce a three dimensional model into an equivalent two dimensional model of Hahn by writing the system in fast-slow settings and choosing a suitable small parameter, allowing us to draw conclusions about the dynamics of the higher dimensional model from the reduced one.

# Mathematical Modeling of Breast Cancer and Optimal Control Analysis of Treatment Strategies

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In this article, a mathematical model of breast cancer governed by a system of ordinary differential equations in the presence of anti-cancer drugs and ketogenic diet is discussed. Several comprehensive mathematical analyses were carried out using varieties of analytical methods to study both local and special case of global stability of the breast cancer model. Also, sufficient conditions on parameter values to confirm the metastasis of cancer in the absence of anti-cancer drugs and ketogenic diet are 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. This is achieved by considering different treatment strategies of administering the anti-cancer drugs and ketogenic diet, using the popular Pontryagin's Maximum Principle. Numerical simulations were presented to validate our theoretical results.

# Impact of Information on the Usage of Pesticide-Treated Bed-nets in the Control of Malaria Disease Prevalence

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Malaria is a major cause of morbidity and mortality in children and adults globally. Many interventions have been proposed and implemented of which insecticide-treated bed-nets play a vital role. The treated bed-nets have been reported to reduce malaria cases by 50%. However, human behaviour and lackadaisical attitude has been an impediment for the effectiveness notably through improper handling and exposure to direct sunlight. In order to address this issue quantitatively, we formulate and analyze a mathematical model which accounts for the effect of individual behavioural response to information on the transmission dynamics of malaria infection in mosquito and human populations. The impact of information on the usage of pesticide-treated bed-nets is investigated as well as the effect of treated bed-net usage on prevalence. Stability analysis of the steady states is performed in terms of the associated basic reproduction number  $R_0$ , a threshold parameter that determines whether the disease dies out or persists in the host populations. Our model assumes that information induces behavioural change in susceptible individuals which results in an increase in the usage of treated bed-nets. Thus, it reduces the basic reproduction number hence the disease burden. In this paper, we identify a threshold for effective reduction of malaria cases via behavioural change in use of ITNs in response to information.

**Keywords:** Behavioural response, Bifurcation, Information/Awareness, Stability

## Phosphoinositides and DGK control of the epithelial sodium channel in cystic fibrosis

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\*Presenter

Cystic fibrosis is a condition caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride and bicarbonate channel. The epithelial sodium channel (ENaC) is also affected, through upregulation of its action. This mechanism is thought to be one of the causes of the thick dehydrated mucus that characterizes the disease, as well as the cause of recurrent pulmonary infections and inflammation that ultimately destroy the lungs of the affected subjects.

Phosphoinositides are rare signaling lipids that constitute a complex network regulating many cellular processes. One of many functions of phosphoinositides is the regulation of cell membrane proteins, and several studies specifically implicate phosphatidylinositol 4,5-biphosphate (PI(4,5)P<sub>2</sub>) in ENaC regulation.

Diacylglycerol kinase (DGK), an enzyme of the phosphoinositide pathway, is known to moderate ENaC function, and this effect could potentially be exploited as a therapeutic in cystic fibrosis. However, the mechanism of DGK moderation of ENaC is not completely understood, although a frequently accepted hypothesis is that DGK influences PI(4,5)P<sub>2</sub> production by halting phosphoinositide recycling.

We have created two models: one of the phosphoinositide pathway and another of ENaC and ASL. Together, these models enabled us to study the roles of DGK and ENaC and strongly suggest that, contrary to the usually accepted hypothesis, this regulation works through the control of PI(4,5)P<sub>2</sub> production by type-I phosphatidylinositol-4-phosphate 5-kinase (PIP5KI) which, in turn is controlled by phosphatidic acid (PA), the product of DGK.

Difference in seasonal variations between transmission rate and re-activation rate explains the epidemic curves of Varicella and Zoster

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Varicella-Zoster virus (VZV) is the causative agent of Varicella and Zoster. The children infected with VZV show Varicella and the re-activation of VZV among individuals recovered from Varicella induces Zoster. Both Varicella and Zoster cases show annual oscillation. Interestingly, the antiphase-relation between epidemic curves of Varicella and Zoster has been observed. To understand the mechanism of antiphase relation, we tested two possible hypotheses: the antiphase relation comes from i) the delay of VZV re-activation due to exposures with VZV (boosting immunity) ii) the difference of seasonal variations between transmission rate and re-activation rate. We found that both hypotheses can induce the antiphase-relation, however, boosting immunity cannot induce the large amplitude of Zoster cases as observed in the epidemic curve of Zoster. The seasonality of re-activation rate with the specific phase is required to explain the antipahse relation between epidemic curves of Varicella and Zoster.

## Systematic analysis of a bifurcating model of tumour-immune interactions

Ana Osojnik<sup>a,1</sup> (presenter), Helen Byrne<sup>a,2</sup>, Eamonn Gaffney<sup>a,3</sup>, James Yates<sup>b,4</sup>, and Michael Davies<sup>b,5</sup>

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Despite clinical successes of immunotherapies, data from trials continue to show patient responses separated into two groups; non-responders whose tumours continue to grow and responders whose tumours shrink or are eradicated. While such observations may be caused by heterogeneity in the tumour microenvironments, they also suggest that a better understanding of tumour-immune interactions is needed to improve response rates to these treatments. In this presentation we will show how mathematical modelling can be used as a tool to gain insights into these complex systems.

We study a five-compartment mathematical model originally proposed by Kuznetsov et al.<sup>1</sup> (1994) to investigate the effect of nonlinear interactions between tumour and immune cells, whereby immune cells may induce tumour cell death, and tumour cells may inactivate immune cells. Exploiting a separation of timescales in the model, we use matched asymptotics to derive a new long-timescale approximation of the full model, which differs from the quasi-steady-state approximation introduced in Kuznetsov et al.<sup>1</sup> (1994), but is numerically validated against the full model. Through a phase-plane analysis, we show that our reduced model is excitable, a feature not traditionally associated with tumour-immune dynamics. Through a systematic parameter sensitivity analysis, we demonstrate that excitability generates complex bifurcating dynamics in the model. These may explain a variety of clinically observed phenomena, and suggest that excitability may underpin tumour-immune interactions. The model exhibits the three stages of immunoediting – elimination, equilibrium, and escape, via stable steady states with different tumour cell densities. Such heterogeneity can stem from variability in initial conditions and/or parameters that control the properties of the immune system and its response to the tumour. We identify biophysical parameter targets that could be manipulated with immunotherapy to control tumour size, and find that preferred strategies may depend on the strength of a patient's immune system, as determined by patient-specific values of model parameters.

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<sup>1</sup>V. A. Kuznetsov, I. A. Makalkin, M. A. Taylor, and A. S. Perelson. Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. *Bull. Math. Biol.*, 56(2):295–321, 1994.

## Understanding zebrafish pigment pattern formation using mathematical modelling

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Animal pigment patterns are of great biological importance, with key roles, for example, in mate selection, predator avoidance, UV protection and temperature control. Adult zebrafish (*Danio rerio*) exhibit a striking blue and gold stripe pattern. As a result of considerable research over the last 20 years, this pattern has become a paradigmatic example of pigment pattern formation. The pattern has been shown to be robustly generated predominantly through the self-organisation of three different pigment producing cell types: yellow xanthophores, black melanocytes and iridescent S-iridophores.

Most research into pattern formation in zebrafish has focused on the roles of melanocytes and xanthophores, so that consequently their interactions and behaviours have been defined in considerable detail. However, recent studies have uncovered the importance of S-iridophore behaviour during stripe generation. S-iridophores undergo pronounced changes in shape and organisation during pattern formation. These result in two distinct classes of S-iridophores, dense and loose; they appear to influence the behaviour of other pigment cell-types nearby, although the precise roles have not been completely defined.

Mathematical modelling has made a major contribution to the understanding of pigment pattern formation. In particular, mathematical representations have been used to show that self-organised systems of interacting cells can produce the types of patterns observed experimentally. However, we wish to assess the extent to which current biological understanding defines a system capable of generating all the key features of zebrafish pigment pattern formation. To address this issue, we present a fully comprehensive agent-based mathematical model incorporating all three pigment producing cell types and all known cell-cell interactions defined to date. For the less-well understood interactions involving S-iridophores, we propose a minimal set of rules based upon published observations of mutants lacking one of the three primary cell types. Combining these rules into a comprehensive mathematical model, we simulate pattern development for WT and various mutants. We demonstrate that in all cases our model shows good agreement, qualitatively and quantitatively, with real fish patterns. Our results determine a set of biological rules for zebrafish pigment pattern formation that are sufficient to explain both the WT and mutant pigment patterns.

C. Subdiscipline area: Developmental Biology

# Pakman: a modular and efficient software tool for approximate Bayesian inference

Thomas Pak<sup>a</sup> (presenter), Ruth Baker<sup>b</sup>, and Joe Pitt-Francis<sup>c</sup>

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The amount of data generated in the biological sciences has risen sharply due to the development of high-throughput experimental techniques. This abundance of data can be used in conjunction with computational models to gain a better understanding of biological systems and make accurate predictions about future behaviour. Bayesian statistics provides a framework for data-driven parameter estimation and model selection, even when dealing with complicated mathematical models. In particular, inferring model parameters from observed data is possible with approximate Bayesian computation (ABC) methods, even when the likelihood function is analytically or computationally intractable.

However, these methods rely on many repeated model simulations, which can be time-consuming. Certain ABC methods, such as the ABC rejection and sequential Monte Carlo (SMC) method, involve a simulation workload that can be parallelised across many computational nodes. A parallel implementation can thus dramatically reduce the time needed to run these methods. Parallel versions of the ABC rejection and SMC methods have been implemented before, but they are architecture- and problem-specific solutions that cannot be used in other contexts in a straightforward manner.

In this talk, we introduce Pakman, a tool for parallel ABC that is designed to be modular, efficient and portable. Pakman is modular at the systems-level, which means that any executable application can be used with Pakman in a “plug and play” manner. This modular framework allows researchers to use their existing software in ABC workloads, without the need to rewrite their code. Moreover, the use of the Message Passing Interface (MPI) standard for parallelisation means that Pakman can be built and used on virtually any parallel computing platform. Thus, Pakman enables researches to leverage all the computational resources at their disposal to fit mathematical models to experimental data in a convenient and efficient manner.

Pakman can be used in a wide range of applications, but the problems that benefit the most from Pakman are those where the model has the following properties; 1) the likelihood is either unknown or computationally intractable, 2) simulating the model is computationally expensive and 3) there is a large quantity of data available for parameter fitting and/or model selection. For example, cell-based models are generally too complicated to study analytically and are computationally expensive to run. On the other hand, modern cell imaging studies easily generate vast quantities of data. Therefore, a potential application of Pakman is to infer parameters for cell-based models of cell competition.

# Impact of Agricultural Tariffs and Trade Wars on Global Land Use: A Dynamic Network Model

Saptarshi Pal<sup>a</sup>(Presenter), Chris.T.Bauch<sup>b</sup>, and Madhur Anand<sup>c</sup>

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The ecological impact of land use changes by human dominated activities is massive. A significant portion of expanding anthropogenic land use is attributed to expanding croplands and pastures for food production. Earlier works have described increasing land-use as a socio-economic problem with complex human-nature coupling and identified drivers as well as inhibitors of farmland expansion at the cost of natural ecosystems. Our goal is to identify and study one socio-political driver of land-use expansion: the Agricultural Trade Network (ATN). This network plays a critical role in land-use problems as more than a quarter of agricultural land resources are accessed through trade. With the current trend of tit for tat tariff escalations and protectionist trade policies among leading economies, major changes in the structure and properties of the ATN are expected in a very short time period making it a potent driver for large scale land-use changes. This leads us to our motivating question: what are the land-use impacts of trade wars?

We build a dynamic network model describing how tariff changes trigger shifts in ATN structures and use the yield data from FAOSTAT to make predictions about corresponding global land use changes. We consider several trade war scenarios, with varying degrees of participation by countries and unique patterns of tariff escalation and tariff distribution. Under the assumption of current global consumption rate we project substantial increase in land-use changes in all the following scenarios: (i) restrictive Trade War (TW) with no contagion (ii) escalating TW with no contagion and (iii) escalating TW with contagion. While factoring in the current trends of increase in consumption and yield rates, we observe regional trends of agricultural expansion in parallel with net increase in cultivated lands and pastures globally. Tariffs placed on agricultural products with no substitute products (e.g China placing tariffs on US soybeans) but replaceable supplier nations (in this case Brazil and Argentina) result in heavier expansion in comparison to tariffs on products with either of the replaceable options. Additionally, certain regions of the globe may become stress points, bearing the increase in land-use corresponding to multiple land intensive products. Our results suggest that in most cases parties not involved directly in a trade war are ones most affected in terms of heavy land use changes as a consequence of it - making the concerned regions analogous to a battlefield in an armed conflict.

## STOCHASTIC MODELING AND ANALYSIS FOR VIRAL INFECTION

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**Abstract:** In this study, we introduce stochastic models for viral infection (like HIV, HBV, HCV) based on the virus release strategy (budding and bursting), incorporating cell-free and intercellular transmission with the consideration of humoral immune response. The Itô stochastic differential equation (SDE) models are constructed using the property of linear transformation for multivariate normal distribution and the theory of continuous-time Markov chain (CTMC). The stochastic means and standard deviations for the model variables are calculated and compared with the results from the deterministic model. Further, using the theory of multitype continuous-time branching process, we calculate the probability of virus extinction in the stage of disease persistence. This probability is dependent on the initial viral load. The chance of disease elimination is greater in the case of budding than in the case of bursting.

## Avoiding treatment of Hashimoto's thyroiditis: thyroid cancer initiation and growth

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Hashimoto's thyroiditis (HT) is an autoimmune disorder that drives the function of thyroid gland to the sequential clinical states: euthyroidism (normal condition), subclinical hypothyroidism (asymptomatic period) and overt hypothyroidism (symptomatic period). Consequently, serum thyroid-stimulating hormone (TSH) levels increase monotonically, which stimulates the thyroid follicular cells chronically and initiates the benign (non-cancerous) thyroid nodules at various sites of the thyroid gland. Due to prolonged TSH stimulation, thyroid nodules may grow in different sizes and become suspicious or malignant (cancerous) without the administration of treatment. When the nodule size is larger than 1 cm in diameter, the occurrence of thyroid cancer is very well possible. Typically, papillary thyroid cancer or thyroid lymphoma is associated with Hashimoto's thyroiditis. A stochastic model is developed in this article to produce the statistical distribution of thyroid nodules growth and cancer incidence by taking serum TSH value as the continuous input from the patient-specific deterministic model developed for the Hashimoto's thyroiditis.

## Model-driven experiments induce elimination of *Staphylococcus aureus* chronic infection

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*Staphylococcus aureus* is a hazardous bacterium, which is responsible for nosocomial- and community-acquired infections globally. It is notorious for its multidrug resistance, which leads to recurrent or chronic infections, and even life-threatening diseases. In chronic infections, the presence of a population of cells that suppress the function of T cells helps the persistence of the bacterium. These cells are known as Myeloid Derived Suppressor Cells (MDSC) and they consist of heterogeneous groups of immature myeloid cells. In this study, our mathematical model sheds light onto whether the expansion of the MDSC during chronic S. aureus infection takes place in the site of infection or systemically. We conclude that the origin of the proliferation is predominantly systemic, and our conclusion is validated by experimental data. Further analysis of the model suggests perturbation approaches to destabilize such chronic infection equilibria in the system, which could induce clearance. Experiments following up these mathematical predictions were conducted and experimental results confirmed the model-driven suggestions revealing MDSC reduction, recover of T cell function and complete clearance from S. aureus.

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## Maximizing Tumour Killing and Minimizing Neutropenia to Optimize Chemotherapy Regimens

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Chemotherapy regimens aim to remove cancerous cells by disrupting cellular division. Unfortunately, due to the generalized nature of cytotoxic chemotherapy drugs, a frequent side-effect of anti-cancer treatment is a severe depletion of the number of circulating neutrophils that make up a crucial component of the innate immune response to pathogens. Neutropenia (a lack of neutrophils) acquired during chemotherapy may require treatment adaptations, including the complete interruption of therapy. To offset these disruptions, exogenous granulocyte colony-stimulating factor (G-CSF), the principal cytokine regulating neutrophil production, is administered to increase neutrophil counts during chemotherapy. We will show how the use of G-CSF during cytotoxic chemotherapy can be optimized by considering simple models of tumour growth together with our previously-developed model of neutrophil production. We consider optimized regimens those that best minimize neutropenic episodes while maximizing the anti-cancer effects of chemotherapy. Our approach thus balances treatment tolerability and efficacy, providing appreciable reductions to the overall drug burden and significant benefits to patient outcomes.

# The Goldilocks Window of Personalized Chemotherapy: An Immune Perspective

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The immune system is increasingly being recognized for its untapped potential in being recruited to attack tumors in cancer therapy. The main challenge, however, is that most tumors exist in a state of immune tolerance where the patient's immune system has become insensitive to the cancer cells. In order to investigate the ability to use chemotherapy to break immune tolerance, we created a mathematical modeling framework for tumor-immune dynamics. Through a system of ordinary differential equations which were calibrated through clinical and experimental observations, our framework simulated the effects of repeated rounds of chemotherapy. We explored chemotherapeutic dosage declines and variations in patient immune parameters to determine the most effective dosing for tumor reduction. Our results suggest that optimal chemotherapy scheduling must balance two opposing objectives: maximal tumor reduction and preserving patient immune function. Successful treatment requires therapy to operate in a Goldilocks Window where patient immune health is not overly compromised. By keeping therapy just right, we show that the synergistic effects of immune activation and chemotherapy can maximize tumor reduction and control. This framework offers a unifying paradigm for explaining clinical observations of the antagonistic impact of chemotherapy when combined with immune activation-dependent treatments. It suggests there should be a reexamination of the maximal dosing intuitions which are prevalent in much of cancer therapy.

## Coupled oscillators in the gut

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The entire length and circumference of the gut, an area of  $0.7 \text{ m}^2$  in the human, is lined by a web-like network of coupled, oscillating cells. These cells are the interstitial cells of Cajal of the myenteric plexus (ICC-MP). The membrane potential of each ICC oscillates independently of all the others, but as the ICC are coupled by electrical gap junctions their oscillations synchronise into phase waves. Each electrical phase wave excites the muscle, producing a corresponding wave of contraction. There is a gradient in the natural frequency of the ICC such that the electrical/contraction waves appear to travel down the gut from stomach to anus - this is important as food should generally be propelled in this direction rather than the reverse. Synchronization also means that wave frequency, rather than decreasing smoothly down the intestine, is pulled into a series of "frequency plateaux" separated by steps. This much was known until recently. We have added to this picture by examining the space-time patterns of ICC-MP contraction waves in the mouse gut. Every  $n^{th}$  wave terminated at a frequency step, where  $n = \text{wave frequency}/\text{step size}$ . Each termination or "dislocation" was followed by a comet-shaped increase in wave interval. It is these discrete and quantal "interval waves" that make up the measured frequency "plateau". Dislocations and their interval waves were reproduced in a toy model consisting of a 1-D chain of weakly coupled phase oscillators. The model suggested that step location was determined dynamically by a balance between stochastic coupling variation and pulled-natural frequency difference. This was demonstrated experimentally with gap junction blockers and localised pinch decoupling. Also the model suggested that natural frequency varies stochastically about its gradient, causing the formation of v-waves at short plateau lengths. We measured the phase response curve and state-space foliation of the ICC-MP using electrical field stimulation. This showed that the dislocation corresponds in state-space to the slow manifold foliation about the equilibrium point at the centre of the limit-cycle. In conclusion, experiment and model have revealed the rich emergent behaviour of a simple network of biological coupled oscillators.

## Why fast-growing bacteria carry more DNA of viral origin

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Temperate bacteriophages are a class of viruses that undergo two possible life cycles. In the lytic life cycle, the virus infects and kills a host bacterial cell, releasing a large number of progeny into the environment. The viruses may however undergo a lysogenic life cycle, in which the virus integrates its genome into the host cell DNA; a new copy of the viral genome is then produced when the host bacterium proliferates. Since the lytic life cycle seemingly confers an immediate advantage, conditions under which the lysogenic life cycle is favoured have long been debated [2]. A recent study of over 2000 bacterial genomes revealed the puzzling relation that the minimal doubling time of a bacterium is strongly correlated with the probability of lysogeny [3]. It has also been suggested that “fast-growing” bacteria are favoured in environmental conditions that widely vary over time [1]. Here, we extend a model developed in our previous work [4], analysing a system of ordinary differential equations that includes three compartments (hosts, infected hosts, and free virus) where the carrying capacity is a periodic function of time. We are then able to simulate a variable environment by manipulating the period and amplitude of this periodic function. The results of a pairwise-invasibility analysis demonstrate that the evolutionarily stable probability of lysogeny increases with environmental variability. This suggests that both lysogeny and short doubling times are favoured in variable environments, offering a novel explanation for the observed correlation between the two factors.

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## $\beta$ Cell Network Dysfunction in Pancreatic Islets by Silencing Hub Cells

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Pancreatic  $\beta$  cells are responsible for secreting the hormone insulin, a key player in the homeostasis of blood glucose levels that improperly regulated can lead to diabetes. Organized in clusters of cells called the islets of Langerhans,  $\beta$  cells in healthy patients have coordinated, pulsatile activity attributed to gap junctions coupling neighboring cells. Recent experimental work has shown that silencing special “hub” cells can lead to a disruption in the synchronous behavior of the islet, calling into question the democratic paradigm of islet secretion with more or less equal input from each  $\beta$  cell. With a network structure of cells (nodes) and gap junctions (edges), we have attempted to replicate this hub cell hypothesis with a mechanistic model representing the electrical and calcium dynamics of  $\beta$  cells during insulin secretion. We can build functional connectivity networks from the simulated calcium traces, leading to the characterization of some networks as scale-free. Following from the hub-follower property of scale-free networks, potential hub cells are identified using centrality measures. Their activity is silenced and the impact on the islet is measured with synchronization indexes and functional connectivity. Specific conditions are required on the network construction to replicate the breakdown of synchrony, raising questions into the robustness of the hub cell hypothesis.

## Modelling the Dynamics of Hematopoietic Stem Cells.

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Mathematical models of hematopoiesis (blood-production in the human body) provide insights into the processes behind hematopoietic malignancies, such as acute myeloid leukemia (AML) or the myeloproliferative neoplasms (MPNs).

Andersen et al (2017) introduces a mechanism-based model of the development of MPNs through a system of ordinary differential equations. The model describes the dynamic behaviour of both normal (healthy) and mutated (MPN) hematopoietic cells, coupled through a novel type of inflammation-dependent feedback.

Present work seeks to extend and improve the model through careful considerations about the behaviour of the hematopoietic stem cells (HSCs) in the bone marrow micro-environment.

HSCs are assumed to bind to certain niches in the bone marrow in a reversible fashion. Understanding how this binding influences the dynamic behaviour of malignant stem cells could be crucial for understanding malignancies arising from HSCs, such as MPNs.

Investigating the HSC/niche dynamics through a stand-alone model yields insights on its own. In particular, by estimating model-parameters based on data from the literature, we hypothesize how certain mechanisms included in the model influence the behaviour of the HSCs. Incorporating these results into a larger model of the entirety of hematopoiesis allows for more accurate fitting with patient-data, and in particular, better understanding of the prerequisites for efficient treatment.

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## A System Biology Approach to Study Anti-PD-1 Cancer Immunotherapy

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PD-1 (programmed cell death protein 1) is a cell surface molecule that is exhibited on many cell types, including cancer cells and activated T lymphocytes. When PD-1 is engaged by its ligands, e.g. PD-L1, activated T lymphocytes are inhibited. However, anti-PD-1 immunotherapy treatment has shown both positive and negative results in terms of its ability to inhibit tumour growth. In this work, a systems biology approach is used to analyze the immune systems response to anti-PD-1 treatment of multiple head and neck cancers by considering key T lymphocyte subpopulations and their dynamics in response to anti-PD-1 treatment. The model is validated with available data, and sensitivity analysis is applied to identify the key phenomena involved in developing resistance to anti-PD-1 treatment so that responders and non-responders can be differentiated.

## Tracking *P. aeruginosa* transmission routes in intensive-care units using mathematical models

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**Context:** Hospital-acquired infections remain a major cause of morbidity and mortality worldwide particularly in immunocompromised patients. Stochastic epidemic models may be used to discriminate different transmission routes and to quantify their relative importance in ICUs. For *Pseudomonas aeruginosa* (*P. A.*), environmental contamination is suspected to play an important role in the transmission process. Many existing methods that quantify the impact of contaminated surfaces rely on deriving specific values for parameters from the literature. The challenge remains in utilizing and integrating only data routinely collected in ICUs, e.g. screening and antimicrobial susceptibility testing results.

**Objectives:** Using only routine surveillance data, we estimate the relative importance of the transmission routes of *P. A.* in two ICUs of the University hospital of Besançon (UHB, France). In particular, we are interested in the contribution of environmental contamination after discharge. Our second aim is to explore the added value of antimicrobial susceptibility tests on our analysis.

**Methods:** We use stochastic SI models and Bayesian data-augmented MCMC methods to estimate the relative contributions of different routes: background transmission (e.g. due to antibiotic selection pressure), cross-transmission, and environmental contamination after the discharge of patients. First, the analysis is performed using only longitudinal surveillance data. Second, we incorporate information derived from antibiograms. Additionally, we perform simulation studies to assess the influence of the quality of the screening data on the certainty of our estimates. Finally, we discuss model selection and model assessment - often overlooked steps in model building for infectious diseases.

**Results:** Background and cross-transmission account for a similar proportion of transmissions of *P. A.* in the two ICUs of UHB, i.e. 55% (cri: 41 – 69%) and 44% (cri: 28 – 58%) respectively. Only about 1% of the transmissions were due to environmental contamination after discharge. The uncertainty in the estimates is expected to be reduced by integrating information on antibiotic susceptibility testing.

**Conclusion:** Improved cleaning of the environment after the discharge of patients may have only a limited benefit regarding the transmission of *P. A.* in the two ICUs of UHB.

## Early-warning signals of epidemics in a multiplex disease-behaviour model

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Resurgences of vaccine-preventable diseases in many countries have overwhelmed public health systems, interrupted tourism and public services and decreased GDP through the huge costs of large-scale interventions. These events have been driven by falling vaccination rates; this is due to the spread of vaccine distrust, facilitated by the ease of spreading questionable content on social networks. This, combined with users explicit ability to choose their social contacts on these networks, makes it difficult to effect any mass changes in sentiment beneficial to public health.

The negative effects of these outbreaks can be mitigated through the use of predictive tools to coordinate preventative interventions. This close relationship between social and disease dynamics suggests that patterns of social interaction may be used to predict these epidemics. Early-warning signals, easily recognisable and statistically significant behaviours that precede phase transitions in physical systems, have shown promise as methods for quantifying these predictions.

An multiplex agent-based simulation was used to model the spread of a vaccine-preventable disease in a randomly networked population with different initial proportions of vaccinators. Parameters representing the imposition of social norms and the perceived risk of vaccination were varied, with nodes reevaluating their vaccine sentiment upon social interaction with dissenting contacts.

Results yielded various metrics such as the join count and spatial autocorrelation coefficients, that predicted epidemics through monitoring the connectivity of the social network and synchronisation of network dynamics. This work makes a unique contribution to the current literature surrounding coupled disease-behaviour systems and early-warning signals, and will provide a basis for future work in the area.

## Modeling the Heroin Epidemic

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A report will be given on the formulation of a heroin/fentanyl epidemic model. This model, consisting of a system of ordinary differential equations, aims to better understand the dynamics between regular prescription opioid use, opioid addictive use, heroin/fentanyl use and recovery from opioid addiction.

## Quantifying Kinetic Differences in Two Recombinant Parainfluenza Viruses

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Human parainfluenza viruses (HPIVs) are a leading cause of a acute respiratory infection hospitalization in children under 5 years, yet little is known about the dynamics of HPIVs infections. To understand and quantify HPIV infection, we utilized bioluminescence data from mice infected with either a high or low dose of one of two recombinant parainfluenza viruses, which exhibit either an attenuated and wild-type phenotype. Both viruses increase exponentially, peak, then decay biphasically. We previously described this biphasic decay for influenza virus infection using a mathematical model with density-dependent infected cell clearance. We fit this model to the parainfluenza infection data to identify the kinetic differences between the two recombinant viruses and between the two doses. We then used nonlinear mixed effect modeling to further assess individual heterogeneity. Fitting the model to the data indicated that the two viruses differ in their viral production rates and nonlinear infected cell clearance rates. As expected, the attenuated virus had a lower rate of virus production compared to the wild-type virus. The duration of infected cell clearance was shorter with a higher infected cell saturation limit for the attenuated virus than the wild-type virus, potentially indicating differing levels of infection clearance ability of the host in each condition. These results quantify parainfluenza virus infection and yield insight into how the rates of virus growth and decay change with different viruses and with different doses.

## 1 Subdiscipline area

Immunobiology and Infection

# Comparing strategies for HIF-1 activation in a fluctuating hypoxic environment

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Growing tumors are complex ecosystems of cancer cells with dynamic microenvironments. Within the tumor ecosystem, cancer cells will experience acute or chronic hypoxia due to excessive disorganized vascular growth. Tumor hypoxia is a poor prognosis factor because it leads to the development of treatment resistant cells. Cancer cells, like all cells, possess mechanisms to respond to heterogeneity in the supply of oxygen, including cell cycle arrest, concomitant decrease in oxidative phosphorylation and increase in glycolysis, and the secretion of angiogenic factors to promote blood vessel formation.

The transcription factor hypoxia-inducible factor 1 (HIF-1) is largely responsible for mediating a cell's response in hypoxic environments. HIF-1 activation is typically facultative, induced by hypoxia and reduced by normoxia. As seen in the development of some tumors, the expression of HIF-1 switches from a facultative state to a constitutive state, where HIF-1 expression increases regardless of the environment. This is known as *pseudohypoxia*. Either way, an increase in HIF-1 activation is a tradeoff. Under prolonged hypoxia without stabilization of HIF-1, cells will die. However, under normoxia, accumulating HIF-1 comes at a cost. Accumulation of HIF-1 in a well oxygenated environment entails using energy for the synthesis of proteins that are HIF-1 induced.

We developed a mathematical model with the goal of determining the optimal level of HIF-1 expression with respect to differences in oxygen availability. Specifically, we seek to answer what may cause the evolution of a change from facultative to constitutive or "hard-wired" HIF-1 expression. In silico simulations were used to define how a cell would express HIF-1 in response to instantaneous depletion and restoration of oxygen within the tumor microenvironment. Results from the model show that environments where a cancer cell experiences longer cycling times between periods of normoxia or hypoxia select for an inducible expression of HIF-1. Whereas frequent fluctuating oxygen levels lead to indistinguishable changes in the upregulation and downregulation of HIF-1, exhibiting constitutive HIF-1 expression.

# A systems biology approach to study adaptive drug resistance in acute myeloid leukemia

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Bcl-2 over-expression is a common survival mechanism for several types of cancer, including acute myeloid leukemia (AML), and it is often associated with poor prognosis. Bcl-2 specific inhibitors can sensitize cancer cells to apoptosis and they have shown promise in recent clinical studies as a targeted treatment option for patients with relapsed/refractory AML. However, monotherapy with Bcl-2 specific inhibitors in AML is often accompanied by the rapid development of drug resistance. It was recently discovered that the acquired drug resistance can be overcome by treatment with the inhibitor in combination with the antibiotic Tedizolid, and this is believed to be a consequence of activating the integrated stress response (ISR). Here we use a systems biology approach to acquire a deeper understanding of this molecular mechanism and, in particular, of the role of the ISR in the commitment of cancer cells to apoptosis. Specifically, we develop a mathematical model of the ISR coupled to the intrinsic apoptosis pathway and simulate the effects of combination therapy on the coupled pathway. We validate the model using genetics data (RNA sequencing), proteomics data (Western Blot and Flow Cytometry), and CRISPR knockout experiments. We perform a sensitivity analysis to measure the robustness of the model to perturbations in the parameter values. Finally, we simulate the system under different initial conditions and treatment schedules to determine the most efficient treatment protocol.

## Inferring population dynamics from high-throughput sequencing

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High-throughput sequencing provides access to expression-level detail of cell populations. Identifying signal in this data is nevertheless a challenge: intrinsic variability, vast subsampling, and indirect access together make difficult the reliable and accurate inference of the changes in population size due to environmental perturbations. Here, in the context of antigen-perturbed immune cell repertoires, we present a generative model of observed sequence count pairs. For pairs of replicates, our model captures the natural variability in the system, giving reproducible behaviour across donors. Using the replicate model as a baseline, we then learn the parameters of a prior distribution of the ratio of a clone's frequency pair for pairs of repertoires sampled at different timepoints. After validating the model on synthetic repertoire data, we infer the posterior distribution of this ratio for every observed clone. Finally, we use point estimates obtained from the posterior to identify candidate responding clones, which are confirmed in a subsequent functional assay. Our method can be used in the clinic to track disease-specific clones expanding or contracting after infection, vaccination, or therapy.

# Feedforward regulation of nitrate transporter NRT1.1 bifunctional activity depending on soil nitrate availabilities

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\*Presenter

Nitrogen - a nutrient and a signaling molecule - is critical to the biological productivity of the planet, yet it becomes an ecological and aquatic pollutant when too much is present. Defective nitrate signaling in plants causes disorder in nitrogen metabolism and it negatively affects nitrate transport systems that switch between high-and low affinity modes depending on soil nitrate availabilities. However, how the nitrate ion plays dual roles as a signaling molecule and an essential source of nutrient remains a mystery. Recent discovery of a plasma membrane nitrate transceptor protein, a transporter cum a sensor NRT1.1, sheds new light on intertwined molecular mechanisms of nitrate uptake and sensing reliant on intracellular demand and extracellular supply of nitrogen. In this work, we use computational modelling combined with mathematical modeling and proteomic approach to discover an incoherent feedforward regulation of NRT1.1 biphasic activity that are stably adjusted according to the levels of extracellular nitrate concentrations. The results show that upon nitrate binding, intrinsic asymmetries between the two protomers of homodimer NRT1.1 that are further enhanced by nitrate binding differentially affect the calcium-dependent activities of cytosolic kinase complex CBL9.CIPK23 that phosphorylates the NRT1.1 at threonine 101 site at low nitrate concentration. Differential affinity of nitrate binding to NRT1.1 protomers and subsequent dimer coupling/decoupling effects generate two opposite but interacting regulatory signals integrate by a gate function jointly controlling the dynamic phosphorylation state of NRT1.1 thereby establishing a functional toggle switch with bi-stability at low/high nitrate levels. This phosphorylation switch is responsible for switching between high-and low affinity transport modes and biphasic behavior of primary nitrate response (PNR) involving several nitrogen assimilatory and transporter genes. Further, using biophysical techniques we show that the exclusive dynamics of one of the protomers upon dimer decoupling is primarily responsible for high affinity signaling and transportation. These results are expected to enhance our understanding of mechanism of nutrient signaling leading to adaptation and may also serve key inputs in improving nitrogen-uptake-and-use-efficiency (NUUE) of crops.

## Evaluating vaccination strategies for tuberculosis in endemic and non-endemic settings

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According to the World Health Organization, tuberculosis (TB) is the leading cause of death from infectious disease worldwide. While there is no effective vaccine against adult pulmonary TB, more than a dozen vaccine candidates are in the clinical trial pipeline. These include both pre-exposure vaccines to prevent initial infections and post-exposure vaccines to prevent reactivation of latent disease. Many epidemiological models have been used to study TB, but most have not included a continuous age structure and the possibility of both pre- and post-exposure vaccination. Incorporating age-dependent death rates, disease properties, and social contact data allows for more realistic modeling of disease spread. We propose a continuous age-structured model for the epidemiology of tuberculosis with pre- and post-exposure vaccination. We use uncertainty and sensitivity analysis to make predictions about the efficacy of different vaccination strategies in a non-endemic setting (United States) and an endemic setting (Cambodia). In particular, we determine optimal age groups to target for pre-exposure and post-exposure vaccination in both settings.

## Evolution of cooperation on an epithelium

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Cooperation is prevalent in nature, not only in the context of social interactions within the animal kingdom, but also on the cellular level. The production of growth factors by cancer cells can be considered a cooperative function: the producer cell bears a cost, but the benefits are shared with its neighbours. Cell populations are arranged into tissues, such as epithelia, which have a distinctive yet dynamic structure, due to the processes of cell motility, division and extrusion. Evolutionary graph theory (EGT) provides a framework for studying the evolution of cooperation in a population with spatial structure, however it represents this structure with a static graph which cannot accurately reflect the tissue dynamics. Furthermore in order to maintain this fixed structure in EGT it is necessary to couple birth and death processes in an update rule. It is well-established that the choice of update rule is a major determinant of evolutionary outcomes, however it is unlikely that any can provide an accurate representation of cell division and extrusion in a real tissue.

By using a mechanical model of an epithelium- the Voronoi Tessellation model, we have considered the evolution of cooperation in a cell population where birth and death are not spatially coupled. We have calculated fixation probabilities using simulations and an approximate analytical technique and found that this decoupling leads to increased success of cooperation when compared with EGT predictions.

## STRATEGIES IN CONTROLLING GLIOBLASTOMA INVASION

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Glioblastoma multiforme is the most lethal form of brain cancer, with a median survival of about 15 months with the current standard of care. It is characterized by periodic cell switching behavior between rapid proliferation and aggressive invasion to the surrounding tissue. Despite technological advances in clinical care including surgery and radio-chemotherapy, treatment-resistant glioblastoma remains a challenge. Novel approaches in understanding glioblastoma from modeling and computational perspectives to experimental and clinical investigations are greatly needed to design optimized therapies. In this work, a model of intracellular signalling pathway containing miR-451–AMPK–mTOR control linked to the cell cycle dynamics is utilized. Optimal control theory is employed to regulate up-stream signaling pathway via glucose infusion activating miR-451, and control the down-stream pathway to cell cycle via drug infusion enhancing mTOR activities. Optimal control problem is formulated with the objective of inducing restrained cell growth and reducing migration to the surrounding tissues. Concomitant and alternating glucose and drug infusion protocols are explored under different scenarios providing possible anti-invasion therapeutic strategies.

subdiscipline area: Mathematical Oncology

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## Investigating the functional connectivity of the zebrafish retina

**Paul A. Roberts<sup>a</sup>** (presenter), Marvin Seifert<sup>b</sup>, and Thomas Baden<sup>c</sup>

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The retina is the tissue layer at the back of the eye responsible for sensing light and for the initial processing of visual stimuli. While the basic retinal architecture is conserved across vertebrate species, each species retina is unique, having evolved to detect and interpret the visual scenes peculiar to its environment. It is therefore important to study the retinas of species that have received little attention to date, especially those with differing evolutionary histories and visual requirements, both in order to gain a more comprehensive understanding of vertebrate vision and to inform medical treatments. In this work we take a truly interdisciplinary approach, combining cutting edge experimental techniques with the latest theoretical methods. We use multielectrode arrays (MEAs) to record the activity of complete populations of zebrafish retinal ganglion cells over time in response to a variety of visual stimuli. We then analyse these data using a combination of spike sorting, dimensionality reduction and clustering techniques, enabling us to infer the functional connectivity of the zebrafish retina for the first time.

## Using mathematics to investigate the mechanisms behind vision loss

**Paul A. Roberts<sup>a</sup>** (presenter)

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The retina is a tissue layer at the back of the eye that uses photoreceptor cells to detect light. Photoreceptors can be characterised as either rods or cones. Rods provide achromatic vision under low light conditions, while cones provide high-acuity colour vision under well-lit conditions. The term Retinitis Pigmentosa (RP) refers to a range of genetically mediated retinal diseases that cause the loss of photoreceptors and hence visual function. RP leads to a patchy degeneration of photoreceptors and typically directly affects either rods or cones, but not both. During the course of the disease, degenerate patches spread and the photoreceptor type unaffected by the mutation also begins to degenerate. The cause underlying these phenomena is currently unknown; however, several key mechanisms have been hypothesised: oxygen toxicity, trophic factor depletion and the release of toxic substances by dying cells. We have constructed mathematical models, formulated as systems of PDEs, to investigate these hypotheses. Using a combination of numerical simulations and mathematical analysis, we determine the conditions under which a degenerate patch will spread or remain stable and evaluate the degree to which *in vivo* spatio-temporal patterns of degeneration can be replicated by our models. In time, these models could be used to inform treatment strategies.

## Evolution of T-cell receptors in the context of cancer and self-antigens

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T-cell receptors recognize antigens (i.e. short amino acid sequences) presented by cells in order to combat viral infections and other pathologies. Each T-cell clone responds to a different antigen, and therefore the T-cell repertoire is highly diverse. To prevent auto-immunity, this repertoire undergoes strong negative selection against ?self? antigens during T-cell development, leading to a skewed diversity that primarily responds to ?foreign? antigens (e.g. viral). Proto tumor cells initially start out presenting only ?self? antigens typical of their cell-type of origin, since they arise from normal tissue cells. However, oncogenic mutations will cause the antigenic profile of a tumor cell to emerge from the protective shadow of self-antigen privilege. This exposure can occur through production of mutated antigens that appear ?foreign?, or by over-production of self-antigens to a level at which they foment an auto-immune response. The accumulation and diversification of oncogenic strategies (i.e. acquisition of beneficial ?drivers?) is therefore subject to increased exposure to immune attack, particularly in early-stage tumors where broad immunosuppressive strategies have not had time to develop. Here, we use a mathematical model to study how different aspects of tumor progression (cell turnover rate, radial growth rate, mutation rate, vascular density, and tissue density) stimulate different immune responses. These lead to either complete tumor eradication by the immune system, or immunologic escape and tumor growth. In the tumors that do escape, different patterns of heterogeneity emerge (e.g. big bang vs. clonal sweep vs. highly diverse). Additionally, a diversity of T-cell memory is developed over time, which has implications for the viability of future oncogenic alterations.

SMB Subdisciplines: Mathematical Oncology & Immunobiology and Infection

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Title: Predicting Zika Outbreaks Using Statistical Models

Abstract: Multiple types of statistical models were built to predict the number of Zika cases in a given region using historical climate data. The statistical models trained include the Poisson regression model, the quasipoisson regression model, the negative binomial regression model, and the zero-inflated Poisson regression model. The performances of these models were then evaluated using the number of Zika cases observed. The highest performing models were then trained on bias-corrected climate projections to predict future Zika cases in a number of regions in the United States and in South America. The future climate scenario analyzed represent the emissions track that we are currently on in which no significant emissions reduction measures are taken.

Subdiscipline Areas:

Mathematical Epidemiology

Population Dynamics, Ecology, and Evolution

## Developing a left and a right side: bistability in the Lefty-Nodal network

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Vertebrates have characteristic internal asymmetries whose genesis can be traced back to an early asymmetry in the morphogen Nodal. Nodal determines the left-side developmental fate; its relative absence determines the right-side fate. Lefty is an antagonist of Nodal. Early work on this system suggested that Lefty and Nodal functioned as a classic activator-inhibitor pair to induce a Turing pattern. A more recent paper has proposed that patterning is due to a spreading wave of Nodal. We have developed a model for the Lefty-Nodal system, and shown it to be capable of bistability in the absence of diffusion, which is compatible not only with Turing patterning, but also with patterning by a traveling wave mechanism. Interestingly, bistability is obtained even without Lefty, which is consistent with a recent experimental study showing that control of Lefty expression by Nodal is unnecessary to the establishment of the left-right axis. A graphical stability analysis of the model is presented and used to extract simplified models that will form the basis for future studies.

## **Evolutionary footprint of epistasis**

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Variation of an inherited trait across a population cannot be explained by additive contributions of relevant genes, due to epigenetic effects and biochemical interactions (epistasis). Detecting epistasis in genomic data still represents a significant challenge that requires a better understanding of epistasis from the mechanistic point of view. Using a standard Wright-Fisher model of bi-allelic asexual population, we study how compensatory epistasis affects the process of adaptation. The main result is a universal relationship between four haplotype frequencies of a single site pair in a genome, which depends only on the epistasis strength of the pair defined regarding Darwinian fitness. We demonstrate the existence, at any time point, of a quasi-equilibrium between epistasis and disorder (entropy) caused by random genetic drift and mutation. We verify the accuracy of these analytic results by Monte-Carlo simulation over a broad range of parameters, including the topology of the interacting network. Thus, epistasis assists the evolutionary transit through evolutionary hurdles leaving the trace of haplotype disequilibrium. The method allows determining selection coefficient for each site and the epistasis strength of each pair from a sequence set. The resulting ability to detect clusters of deleterious mutation close to full compensation is essential for biomedical applications. These findings help to understand the role of epistasis in multiple compensatory mutations in viral resistance to antivirals and immune response.

## Modeling Spillover Mutations in Zoonoses with Intermediate Hosts

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The World Health Organization describes zoonotic diseases as a major pandemic threat, and modeling the behavior of such diseases is a key component of their control. Many emerging zoonoses, such as SARS, Nipah, and Hendra, mutated from their wild type while circulating in an intermediate host population, usually a domestic species, to become more transmissible among humans, and this transmission route will only become more likely as agriculture intensifies around the world. Passage through an intermediate host enables many otherwise rare diseases to become better adapted to humans, and so understanding this process with accurate mathematical models is necessary to prevent epidemics of emerging zoonoses, guide policy interventions in public health, and predict the behavior of an epidemic. In this paper, we account for a disease mutating in an intermediate host by introducing a new mathematical model for disease transmission. We present a model of these disease dynamics, including the equilibria of the three-species system and the basic reproductive number of the disease, which can be used to predict the behavior of any zoonosis with an intermediate host and assist efforts to protect public health.

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Subdiscipline: Mathematical Epidemiology

## Can phage therapy replace antibiotics?

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† presenter

Antimicrobial resistance is becoming increasingly common and is a major threat to public health. The overuse and misuse of drugs has rendered many antibiotics ineffective at treating infections, prompting the need for alternative approaches. Phage therapy, where bacteriophage are used to treat pathogenic bacteria, is a possible alternative to antibiotic use. However, the evolutionary consequences of phage treatment are unknown. For example, could phage treatment force the pathogenic bacteria to evolve greater virulence, making it even more harmful to the host? In this talk I derive a compartmental mathematical model for phage therapy. I first explore conditions for successful eradication of the bacterial infection. Then, I allow the bacteria to evolve in response to the phage, and investigate how the bacteria's optimal virulence is expected to change.

## Pre-menstrual inflammatory processes in the uterine endometrium

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The uterine endometrium self-destroys and self-repairs during every menstrual cycle in response to varying levels of ovarian hormones. Inflammatory cues are an essential component of this process, and they likely have a role in widespread pathological conditions. Yet they are still incompletely understood. To complement ongoing medical research, we propose a spatially averaged model of the interactions between leukocytes, inflammatory mediators, and tissue destruction in the endometrium immediately before the onset of menstruation. The concentration of ovarian hormones is a key parameter. The ensuing model is studied using asymptotic analysis and numerical parameter continuation. Our model reproduces the delay observed between the pre-menstrual drop in ovarian hormones levels and the onset of menstruation. It also supports the hypothesis that resident cells play a key role in triggering the inflammatory response, and allows the exploration of the relative importances of resident cells and leukocytes in producing pro-inflammatory mediators. This study aims at bridging the gap towards a complete mathematical model of menstruation and at a better understanding of various underlying mechanisms. Our ambition is to eventually turn menstrual bleeding patterns into a relevant health indicator.

## Mathematics Provides Insight into Self-Organization in Biology

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In this talk we will consider how mathematical modeling, analysis, and simulation can be used to provide new insight into biological phenomena. In particular, we focus on the self-organization of large-scale groups of insects and bacteria. What makes this problem interesting is that individual interactions at the microscale lead to the onset of mesoscale and then macroscale patterns. In addition, when animals exhibit collective behavior one can observe remarkable properties such as enhanced movement speed, pattern formation, and increased mixing. A deep understanding of how and why these properties emerge is fundamental to pressing biological problems such as the design of microscale devices and biomaterials, treating algal blooms in Lake Erie, or preventing neurodegenerative diseases. Throughout the talk we will use mathematics to explain the underlying mechanisms that lead to these incredible features.

## Network Analysis of Eye-Gaze Pattern in Autism

**Mehrshad Sadria** (presenter)<sup>a</sup>, Soroush Karimi<sup>b</sup>, and Anita Layton<sup>c</sup>

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**ABSTRACT:** Individuals suffering from autism spectrum disorder (ASD) exhibit impaired social communication, which manifests in the abnormal eye contact that they make when interacting with others. In this study, we first seek to characterize the spatial and temporal attributes of this impaired eye gaze. To achieve that goal, we analyze and compare eye-tracking data of ASD and typical development (TD) children. Our fixation time analysis indicates that ASD children exhibit a distinct gaze pattern when looking at faces, spending significantly more time at the mouth, compared with TD children, and less at the eyes. Another goal of this study is to identify an analytic approach that can reveal the differences in face scanning patterns between ASD and TD children. Face scanning involves transitioning from one area of interest (AOI) to another, and that process is not taken into account by the classic fixation time approach. To capture such transitions, we apply two network analysis approaches that measure the “importance” of a given AOI: degree centrality and betweenness centrality. Degree centrality yielded statistically significant difference in the mouth as an AOI between the ASD and TD groups, whereas betweenness centrality also revealed statistically significant between-group differences in other AOIs, including the left eye. Thus, our results suggest that betweenness centrality is the most effective network analysis approach in distinguishing the eye gaze patterns between ASD and TD children.

**Sub-discipline area:** Mathematical Neuroscience, Developmental Biology

## Oscillation and Data in a Simple Epidemic Model

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A simple SIR epidemic model for smallpox, with birth and death rates based on historical data, produces remarkable oscillatory dynamics. Sustained oscillations arise naturally from stochasticity and growth in the population data, rather than from a model-imposed structure such as periodic forcing or delay. These natural oscillations display appropriate periodicity for smallpox, as demonstrated via three distinct data sets describing different locations and population sizes. By connecting multiple data sets with a simple model, the underlying autonomous model can be parameterized; overall trends in infectivity can be computed; and demographic data outliers, such as in years of high famine, are shown to have a unique relationship to model oscillation.

## Mathematical modeling to quantitatively evaluate the dynamics of CAR T-cell therapy in glioblastoma

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**ABSTRACT:** Chimeric antigen receptor (CAR) T-cell therapy is an emerging targeted immunotherapy which has shown success in liquid cancers such as leukemias. CAR T-cells are also being used for the treatment of solid tumors such as glioblastoma, which is a primary brain tumor.

Ongoing phase I trials have been designed to evaluate CAR T-cell dosing, scheduling, and route of administration in order to understand and improve the efficacy of CAR T-cell therapy. Investigators at City of Hope National Medical Center were the first to show complete regression of glioblastoma using 1L13R $\alpha$ 2 targeted CAR T-cells, and the first to deliver such therapies to human patients. Based on our unique experience with CAR T-cells for solid tumors, we have identified three critical factors in determining a successful response to CAR T-cell therapy: proliferation, persistence, and killing capacity of CAR T-cells. A better understanding of factors leading to the success of CAR T-cell immunotherapy for solid tumors will be necessary to improve outcomes for patients with solid tumors and to advance the field of CAR T-cell immuno-oncology.

Here we present a simple two-species ordinary differential equation mathematical model which models the interactions between cancer cells and CAR T-cells. Using a novel *in vitro* experimental apparatus, we are able to measure the density of cancer cells over several days in 15 minute interval time resolution. This highly temporally resolved data provides a unique opportunity to confidently estimate parameters of the model and to provide insights into the dynamics of CAR T-cell proliferation, persistence, and killing capacity.

We will show results from experiments using patient-derived cancer cell lines as well as cancer cells engineered to express specific levels of the target antigen (IL13R $\alpha$ 2) to quantitatively evaluate the roles of proliferation, persistence, and killing in cells with different levels of antigen expression. We will discuss the interpretation of the model parameters and demonstrate the clinical value of this analysis through an application of model and simulation-driven optimization of CAR T-cell treatment based upon the unique antigen profile of a given patient's tumor biopsy tissue.

## MODELLING MYELOPROLIFERATIVE NEOPLASMS

### Dynamics of myeloid cell line for Ph-negative MPNs

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Myeloproliferative Neoplasms (MPNs) are haematological disorders characterized by increased proliferation and accumulation of mature myeloid cells in the bone marrow. Mutations in certain genes such as the JAK2 gene, are considered as one of the major causes of Philadelphia-negative MPNs. In addition, it has been claimed that the development of these diseases is strongly influenced by the inflammatory response of the immune system.

In [1], a novel mechanism based mathematical model - the Cancitis model - has been presented consists of a system of non-linear differential equations. The cellular interaction between stem cells and mature cells (ensembled each cell type) are included, in addition, the debris of dead cells and inflammatory load are considered. In a recent paper [2], novel treatment strategies have been suggested and the in silico effect of existing treatment.

The clinical data provided by Roskilde Hospital for three Ph-negative MPNs: ET, PV and PMF is evidence of high blood cells count, especially, platelets for ET, erythrocytes for PV and platelets, erythrocytes and granulocytes for PMF patients. Hence, it inspired us to make an extended version of Cancitis model which is currently under investigation focussing on individual cells of myeloid cell lineage. To our knowledge the model is unique in a sense that it consists of both healthy and abnormal cells and their corresponding growth factors boosting the over-production of mature cells of myeloid branch.

This talk will aim to illustrate a complete analysis of steady states and their stability. It follows the effects of Epo stimulating the formation of normal red blood cells and progressing the abnormal red blood cells as well. A quasi steady state approximation is assumed to hold for Epo concentration, hence the model can be divided into two sub systems i.e. stem cells and erythrocytes. Furthermore, bifurcation analysis will enable us to predict promising treatment strategies for MPNs patients. Finally, the model will be evaluated by comparison to patients' data.

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- [2] Ottesen et al., (2019). Bridging blood cancers and inflammation: The reduced Cancitis model, Journal of Theoretical Biology 465 (2019) 90–108.

## The Tick-Tock of the Molecular Clock: A Story from the Crypt

Ryan O. Schenck<sup>a,†</sup>, Ester Gil-Vazquez<sup>b</sup>, Paulina Siejka-Zielinska<sup>c</sup>, Chun-Xiao Song<sup>d</sup>, Simon Leedham<sup>e,‡</sup>, Alexander R.A. Anderson<sup>f,‡</sup>, and Darryl Shibata<sup>g,‡</sup>

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The small intestinal and colon crypts are hierarchical, dynamic systems. Small numbers of stem cells give rise to daughter cells which proliferate within the transient amplifying zone, giving rise to a differentiated cell population. Stem cell numbers are constant, but survival is stochastic because divisions may result in renewal, expansion, or extinction. This hierarchy is largely maintained even in the face of disease and early dysplasias, where the microenvironment strives to re-establish homeostasis. Surprisingly, little is known about the stem cell numbers within these crypts. By exploiting the hereditary information passed on to each daughter cell during somatic division from whole genome sequencing and methylation data paired a multiscale agent based model we hope to better understand the dynamics of the stem cell pool. Most notably, using this method we can determine the number of stem cells and estimation of the error rates associated with DNA methyltransferase during cell division. The model splits the crypt into two compartments, the base and body of the crypt, and incorporates base pair resolution genomes and CpG sites. We calibrate our exclamationary bowel model with normal human small intestinal and colon crypt data using Approximate Bayesian Computation. This approach provides numerous insights into the dynamics of aging and underlying diseases within human crypts. In addition we hope use our calibrated model to understand why small intestinal crypts rarely develop cancers while colon cancer is frequently seen.

## Contagion dynamics on adaptive networks: Norovirus as a case study

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Classical contagion models, such as SIR, and other infectious disease models typically assume a well-mixed contact process. This may be unrealistic for infectious disease spread where the contact structure changes due to individuals' responses to the infectious disease. For instance, individuals showing symptoms might isolate themselves or individuals that are aware of an ongoing epidemic in the population might reduce or change their contacts. Here we investigate contagion dynamics in an adaptive network context, meaning that the contact network is changing over time due to individuals responding to an infectious disease in the population. We consider norovirus as a specific example and investigate questions related to disease dynamics and applications to public health.

- The subdiscipline area is Mathematical Epidemiology.

## Handguns and Hotspots: Spatio-Temporal Models of Gun Crime in Chicago, Illinois

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Gun violence is a major public health crisis in the United States, annually costing \$229 billion and resulting in the deaths of 31,000 individuals. It has often been compared to an epidemic, communicated through social networks, media presence, and spillover between geographic areas. In this model, we use cellular automata to observe and predict the spatio-temporal spread of gun crime in Chicago, Illinois. The model incorporates significant socio-economic conditions, geographic information systems (GIS) data, and data-informed transition rules. This model can then be extended to determine when and where interventions should be deployed in order to minimize gun crime in Chicago.

## Examining the plankton paradox with timescale-specific predictors of abundance changes

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The “paradox of the plankton” is the name given to the problem of how diversity is maintained in ecological systems where many of the species appear so similar that they should be subject to competitive exclusion. We apply novel statistical methods to detect differences between individual phytoplankton species which may permit coexistence. Earlier work on annualized measures of the level of green phytoplankton growth in the North Sea, as recorded by the Continuous Plankton Recorder (CPR) survey, was able to identify drivers of spatial synchrony by building a timescale-dependent statistical model of the fluctuations using the Morlet wavelet transform. This wavelet modeling approach uses complex coefficients to incorporate any observed phase shifts, resulting from time delays, rate dependencies, or negative correlations, between each driver and the corresponding fluctuations in the response variable. The fact that Morlet wavelet coherences depend on Fourier cross spectra permits fast significance testing of timescale-dependent relationships (coherence) between variables. We exploit this approach to efficiently test which explanatory variables provide statistically significant additional explanatory power to a model of an individual plankton species incorporating the overall plankton colour index; ie. what factors drive the differences between this species and the bulk plankton. We show that there are short term fluctuations in particular species associated with particular climatic and predation factors, rendering them semi-independent of the bulk plankton variability. By means of different sensitivities to environmental factors and predation effects which vary spatiotemporally, species can coexist.

## Coalescent model of imputation accuracy

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Genotype imputation has become an indispensable step in human genetic studies including fine-mapping and meta-analysis. Statistical imputation infers missing genotype in large scale studies with low-cost genotyping, by first identifying an individual from a reference panel with high resolution genotyping that is genetically closest to the target sample and then borrowing information from this closely related individual. With increasingly large genome sequencing data, imputation is able to recover rare variants with minor allele frequencies less than 0.1% in the population. Such rare variants account for a large proportion of genetic variation and can have large effect on human diseases, but they suffer from lower imputation accuracy compared to common variants. Empirical performance of imputation methods has been extensively studied, while the theoretical basis of imputation accuracy has not been well understood.

We develop a coalescent model that enables quantitative analysis and theoretical prediction of imputation accuracy under current genotype imputation framework. It quantifies the inevitable error rate inherent in the procedure due to the genetic distance between the reference genome and the target sample, assuming the genetically closest templates in the reference is correctly identified. Thus our method provides the theoretical upper bound of imputation accuracy given a particular reference panel.

Our results demonstrate how the probability of misspecifying a minor allele decreases with larger reference panel and higher allele frequency. On the other hand, the probability of having uncertainty in identifying the best template individual is independent of the reference size. With probability 1/3, there are multiple individuals in the reference all being the closest to the target, further increasing the uncertainty about imputed genotypes. This analysis of accuracy needs to be taken into consideration when developing new imputation algorithms or when interpreting downstream association analysis.

## Effects of Alignment on Contact Dependent Cell-Cell Interactions

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Colonies of *E. coli*, when grown in a monolayer, are known to spontaneously self-organize, transitioning from a disordered colony to one where the cells are aligned in one direction. The subsequent increase in packing efficiency has the potential to affect contact based cell-cell interactions. We used agent-based and partial differential equation (PDE) simulations to investigate the role this alignment plays in two contact dependent processes: plasmid transfer and contact-based killing via the type VI secretion system. Our agent-based simulations were carried out using the CellModeller software package, which realistically represents cell morphology and physical interactions (in contrast to simpler cellular automaton models). Alternatively, we spatially coarse-grain the system to arrive at a system of partial differential equations. Standard coarse-graining approaches account for local cell density, while local orientation is described using the tensor order parameter, borrowed from the theory of liquid crystals. These simulations accurately capture colony dynamics, and reveal the role of cell morphology (and consequent ordering) on colony-level cellular growth and interactions.

## Unbiased on-lattice domain growth

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Domain growth is a key process in many areas of biology, such as the growth and shrinkage of tissue and neural crest cell migration. As a result, mechanisms for incorporating this into traditional models are of great importance. Previous methods that have been used in order to include domain growth to on-lattice reaction-diffusion models cause a build up of particles on the boundaries of the domain, which is particularly obvious when diffusion is low.

We will firstly discuss why this happens, and proceed to demonstrate the effect in several different ways. Following this, we propose a new method, coined the stretching method, that is correct even in scenarios where the previously accepted method fails. Finally, we compare the original and stretching methods by applying them to two different reaction-diffusion problems.

## An intracellular model linking iron metabolism to the cell cycle

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Iron is a cofactor for crucial cellular processes such as DNA replication and cellular respiration. Breast cancer cells have a peculiar iron-addictive phenotype, and keeping iron away from cancer cells has resulted in cell cycle arrest and apoptosis. However, how iron metabolism and the cell cycle are connected remains poorly understood. We are developing a computational model to study how breast cancer cells acquire iron and how they utilize this iron to progress through the cell cycle. We will present our current model, and discuss how we plan on utilizing this model for a 3D tumor model incorporating different cell types to study the role of iron in cancer growth.

# From fixation probabilities to $d$ -player games: an inverse problem in evolutionary dynamics

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The probability that the frequency of a particular trait will eventually become unity, the so-called fixation probability, is a central issue in the study of population evolution. Its computation, once we are given a stochastic finite population model without mutations and a (possibly frequency dependent) fitness function, is straightforward and it can be done in several ways. Nevertheless, despite the fact that the fixation probability is an important macroscopic property of the population, its precise knowledge does not give any clear information about the interaction patterns among individuals in the population. Here we address the inverse problem: From a given fixation pattern and population size, we want to infer what is the game being played by the population. This is done by first exploiting the framework developed in FACC Chalub and MO Souza, J. Math. Biol. 75: 1735, 2017, which yields a fitness function that realises this fixation pattern in the Wright-Fisher model. This fitness function always exists, but it is not necessarily unique. Subsequently, we show that any such fitness function can be approximated, with arbitrary precision, using  $d$ -player game theory, provided  $d$  is large enough. The pay-off matrix that emerges naturally from the approximating game will provide useful information about the individual interaction structure that is not itself apparent in the fixation pattern.

# Fitness differences between drug resistant and sensitive strains of *Mycobacterium tuberculosis*

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10 million people became infected with tuberculosis (TB) worldwide in 2017. 558,000 of these cases were drug-resistant, while the treatment success rate for drug-resistant TB was only 55%. To understand the epidemic potential of resistant tuberculosis, a key consideration is the effect of fitness on prevalence. Many existing population-level models for transmission of resistant tuberculosis either do not include pathogen fitness or assume that it is fixed. These assumptions obscure the underlying biological reality that pathogen fitness affects the outcome of infections, and that it varies with strain and treatment. A few recently published models of TB transmission have included functions that track distributions of fitness costs. However, multi-scale modeling that explores within-host fitness dynamics within the framework of population-level models is essential. We examined the fitness of *Mtb* in host environments that varied according to the presence or absence of infection with two different *Mtb* strains, and according to the presence or absence of treatment with antibiotics. We developed a mathematical model to assess the effects of a range of fitness values on TB transmission and prevalence, where fitness is defined as a relative cost ( $0 < w < 1$ ) or a relative advantage ( $1 < w < 2$ ). Using this model, we simulated scenarios in which sensitivity or resistance to antibiotics confers costs or advantages. One surprising result of this study is that in some environments, drug-sensitive *Mtb* appears to have an evolutionary advantage over drug-resistant *Mtb*.

## On the probability distribution of resource allocation strategies in plants

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We often view resource allocation in plants as a problem of optimisation. In allocation optimisation models we observe an objective function that takes the role of a plant fitness proxy, while various traits are traded-off to find the maximum of this function. However, a limitation of this approach is that it predicts a single, optimal strategy for plants, whereas in the real world we usually observe the coexistence of a variety of alternative plant strategies. Using a model plant subjected to drought as an illustration, we propose an alternative way of modelling plant resource allocation strategies through the use of Maximum Entropy (MaxEnt) principle. We show that instead of finding a single behaviour corresponding to a maximum in fitness, we instead arrive at a probability distribution of multiple possible strategies. Within these strategies, we usually can observe one that we term the likeliest strategy, which we can associate with an objective function. In this way, MaxEnt can be used as a method for describing coexisting plant allocation strategies from a statistical perspective.

**Additional Information:** Elisa Stefaniak is the presenter.

Subdiscipline is Population Dynamics, Ecology and Evolution

## Optimising biopsy scheduling, integrating digital pathology and agent-based modelling.

Roisin Stephens<sup>a</sup> (Presenter), Lucy Hutchinson<sup>b</sup>, Philip Maini<sup>a</sup>, Helen Byrne<sup>a</sup> and Oliver Grimm<sup>c</sup>

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During clinical trials of cancer immunotherapies, patients are monitored by taking an on-treatment needle biopsy, which is compared to a biopsy taken before treatment, to assess drug efficacy. Due to the invasive nature of the biopsy procedure, clinical trial protocols limit the number of biopsies taken to one baseline (pre-treatment) and one on-treatment. Currently, deciding when to take the on-treatment biopsy is based on experience, which can be problematic as it is not known whether the biopsy is being taken at the most informative time point, when the effect of the drug will be measurable if a tumour is responsive to the treatment, and this is particularly the case with cancer immunotherapies. We have developed a pipeline that integrates the analysis of biopsy data with mathematical modelling in order to assess the efficacy of a particular immunotherapy, and predict the optimal time point at which to schedule the on-treatment biopsy. An agent-based model, initialised using baseline biopsy data, captures the spatial dynamics of the tumour immune micro-environment under the action of an immunotherapy which is currently undergoing clinical trials. Using this model, a time-course of tumour-immune dynamics between the baseline and on-treatment biopsy time points can be generated. This data could then be used by clinicians to determine the most suitable time point for scheduling the on-treatment biopsy for a patient cohort. This integrated approach of combining biopsy data with mathematical modelling has the potential to inform the design of clinical studies, optimising the monitoring of patients receiving treatment, such that the clinical data obtained through model-informed biopsy scheduling may provide an improved insight into drug efficacy.

## Modelling and genomics to identify dangerous *Streptococcus pneumoniae* strains

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*Streptococcus pneumoniae* is a major pathogen causing bacterial disease in humans, but its classification into over 90 serotypes means that only partial coverage vaccines are feasible. Vaccines have proven effective, but lead to significant serotype replacement. These factors result in complex and highly variable pneumococcal populations.

Different locations may also have significant differences in their bacterial populations, providing opportunity for strain migration. For pathogenic bacteria such as *S. pneumoniae*, of particular concern is migration of so called 'dangerous' strains, with, for example, multi-drug resistance or high invasiveness, and which we would predict to reach high prevalence in new populations. Combining sequencing technology with dynamical models offers opportunity to measure the diversity in these populations, as well as forecast which dangerous strains will rise in prevalence following vaccination and migration.

Recently, a negative frequency-dependent selection (NFDS) model was proposed to explain the complex balance of pneumococcal strains (Corander et al. 2017, Nat. Ecol. Evol.). This allows us to directly use genomic data to help understand the relative growth of individual strains, in the context of the population of genomes. We use the NFDS principle to identify dangerous strains, and incorporate this in a deterministic model of strain dynamics to predict those that may become dangerous under given time-frames and vaccination strategies. We compare different models of recombination to explore the space of potential new strain variants, and their associated risk in the populations. From this, we are able to create a post-vaccine fitness profile for the pneumococcal strains currently in existence, to gain insight into what kind of diversity is generatable and therefore inform potential vaccination strategy and public health measures.

## Stability analysis of a bulk-surface model for membrane-protein clustering

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Protein aggregation on the plasma membrane (PM) is of critical importance on many cellular processes such as cell adhesion, endocytosis, fibrillar conformation, and vesicle transport. Lateral diffusion of protein aggregates or clusters on the surface of the PM plays an important role in governing their heterogeneous surface distribution. However, the stability behavior of the surface distribution of protein aggregates remains poorly understood. Therefore, understanding the spatial patterns that can emerge on the PM *uniquely* through protein-protein interaction and diffusion is an important step towards a more complete description of the mechanisms behind protein clustering on the cell surface. In this work, we investigate the pattern formation of a reaction-diffusion model that describes the dynamics of a system of ligand-receptor complexes. The purely diffusive ligand in the cytosol can bind receptors in the PM and the resultant ligand-receptor complexes not only diffuse laterally but can also form clusters resulting in different oligomers. From a methodological viewpoint, we provide theoretical estimates for diffusion-driven instabilities of the protein aggregates based on the Turing mechanism. We also obtain the distribution of the size of the protein aggregates and their spatial locations depending on both initial conditions and kinetic parameters using computational methods. Our results suggest that spatial heterogeneity emerges only when the cluster diffusion rates decay as a function of cluster size.

## Information Processing by Endoplasmic Reticulum Stress Sensors

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The unfolded protein response (UPR) is a collection of cellular feedback mechanisms that seek to maintain protein folding homeostasis in the endoplasmic reticulum (ER). When the ER is “stressed” by high protein folding demand, signaling molecules in the ER membrane initiate the UPR. Recent experiments indicate that signaling molecules detect stress by being both sequestered by free chaperones and activated by free unfolded proteins. However, it remains unclear what advantage this bidirectional sensor control offers stressed cells. Here, we show that combining positive regulation of sensor activity by unfolded proteins with negative regulation by chaperones allows the sensor to make a more informative measurement of ER stress. Using a combination of analytical and numerical techniques, we demonstrate that the optimal sensor balances interference due to indirect measurement of unfolded proteins with extension of the operational range of the sensor. These results provide general guidance on how to monitor bimolecular reactions within cells.

# Man vs Machine: *in silico* and *in vitro* comparison of a mechanistic and a machine learning model for guiding cancer treatment

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Treatment schedule optimisation is an important aim of mathematical oncology. We seek to identify strategies for the timing and dosing of single drugs to maximise the probability of a cure, or to at least prolong the time for which the cancer can be controlled. Ordinary differential equations (ODEs) models represent promising candidates for these efforts. They allow formalisation of the mechanistic assumptions about tumour growth, heterogeneity and drug response and are parameterisable even in the light of scarce, high-level clinical data. Strategies inspired or driven by ODEs are currently being tested for the treatment of prostate cancer with abiraterone, and the personalisation of radiotherapy protocols. However, the recent machine learning revolution has opened up an intriguing alternative: Deep learning technologies which integrate large amount of data into highly parametrised phenomenological models have shown great success in steering complex dynamical systems. If they beat chess masters, can they be used to treat cancer?

In the presented study we compare ODE-guided cancer therapy to treatment according to a deep reinforcement learning (DRL) algorithm, first *in silico* and subsequently *in vitro*. We simulate a growing tumour using a simple birth-death-migration, 2-d cellular automaton model (CA) in which cells are either drug-sensitive or drug-resistant. We evaluate a set of six different ODE models characterised by different growth laws (exponential, logistic, Gompertzian), and a DRL algorithm. The models are calibrated based on the data available up to time  $t$  and are used to make a treatment decision for the next time interval  $[t, t + dt]$ . Subsequently, we present preliminary data of the same comparison in an *in vitro* experimental model of PARP inhibitor based treatment of ovarian cancer. Our work contributes towards the integration of different mathematical models for the personalisation of cancer therapy.

## Activation of the integrated stress response: Does it tune or tame?

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The integrated stress response (ISR) is a highly conserved, protective mechanism that regulates protein translation in response to intercellular stress conditions. First discovered in heme-deficient rabbit reticulocyte lysate, the ISR is now known to be activated in response to a diverse range of stress conditions including: heme deficiency, amino acid deprivation, viral infection, and ER stress. Each of these conditions produce a stress-specific signal that activates one of four kinases: HRI, GCN2, PKR, or PERK. These kinases in turn phosphorylate the initiation factor eIF2 causing a simultaneous down regulation of canonical translation and upregulation of stress response genes. In this way the kinases “integrate” diverse stress signals into a shared downstream response.

Previously we showed that competition between active kinase and a translation enzyme for the substrate eIF2 produces a system with a tunable hysteretic switch controlling protein translation. Here we seek to understand how the mechanism of ISR activation influences this response to stress. It is known that each of the four kinases depend on both dimerization and autophosphorylation for their activation. However, the mechanism by which these steps occur varies with kinase and stress signal. In some cases, the signal induces the dimerization or autophosphorylation steps and in others it releases inhibition on these steps. Why are these activation mechanisms distinct despite their obviously shared features? Is this simply the result of divergent evolution allowing the system to produce the same response to multiple types of signal? Or, do the individual activation mechanisms tune the ISR to produce qualitatively different responses depending on the specific stress condition?

To address these questions, we construct a series of non-linear ode models that describe the kinase activation mechanisms as modular components of a generalized activation model. We then challenge each mechanism with various stress dosing regimens to determine how variation in the activation mechanism structure effects its qualitative response to stress. We conclude by discussing our findings in the context of the overall stress response.

## Contribution of Environmental Pathways to the Transmission of *Clostridioides difficile*

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*Clostridioides difficile* (formerly *Clostridium difficile*) is the leading cause of infectious diarrhea and the most frequently identified healthcare associated infection in United States hospitals. *C. difficile* is typically contracted after antibiotic use, when healthy gut microbiota that prevent colonization is compromised. Colonized patients, both symptomatic and asymptomatic, shed *C. difficile* endospores that can survive long periods on surfaces outside the host and are resistant to many commonly used disinfectants. Transmission pathways can include contact with environmental reservoirs of endospores on fomites (surfaces).

This work focuses on the effect of fomite touch frequency on *C. difficile* transmission. The dynamics are modeled using a system of ordinary differential equations representing the classes within the total patient and pathogen populations. Due to the small population size of the considered hospital, we also compare a stochastic simulation of the corresponding events. The results can be utilized to examine the role surfaces with varying touch frequencies contribute to patient colonization of *C. difficile* in healthcare settings.

# On the mathematical form of an incentive in a socio-ecological model

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How does the incentive to take environment-friendly actions influence the possible asymptotic behaviours of a social-ecological system? The example of a model for lake pollution dynamics allows us to discuss this question.

We consider a two-dimensional model of coupled ODEs representing respectively the ecological subsystem (the lake) and a socio-economic subsystem (polluters). The socio-economic subsystem uses the replicator dynamics from evolutionary game theory and is driven by the incentive to decrease the discharge of pollution. This incentive depends on the level of pollution which is observed in the lake and on social pressure.

We explore how the functional form of this incentive impacts the shape of the nullclines and the possible asymptotic regimes. A discontinuity in the incentive, as under the implementation of a new policy, gives rise to a discontinuous nullcline and to new cycles around a pseudo-equilibrium potentially. A pattern where the incentive decreases when the pollution level and/or the cooperation level is too high, as when agents give up on taking environment-friendly actions, may produce a closed curve nullcline.

## MODELING PATTERN FORMATION IN MULTICELLULAR SYSTEMS USING AN OPTICAL GENETIC SWITCH

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Cyanobacteria are able to carry out photosynthesis in very limited light availability, such as near the poles and far below the ocean surface. To facilitate this, they have evolved to adjust their photon harvesting systems according to available wavelength (or color) of light. This optogenetic switch is of interest to synthetic biologists as a potential mechanism to optically control cell behavior in other species. A recently discovered five-gene operon is considered responsible for the switching behavior between blue and green light conditions. To better understand the molecular system responsible for this behavior, we built a mathematical model of the light switch and found that it performs consistently with experimental data. We then used an agent-based PhysiCell model to explore the potential of combining optogenetic and diffusible chemical controls to guide novel spatiotemporal pattern formation.

## Borrowing ecological theory to infer interactions between sensitive and resistant cancer cell populations

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**Background:** While some forms of breast cancer are highly responsive to treatment, endocrine therapy-resistant breast cancers are disproportionately lethal. There has been significant progress in understanding how endocrine therapy-resistant strains evolve from therapy-susceptible strains of cancer, but little is understood about the proliferation of resistance through cancer cell populations.

After the development of drug resistance, the relationship between the new resistant cells and surrounding (drug susceptible) tissue can be understood as an ecological process. The resistant strain and the neighboring susceptible strain are, together, the cancerous tissue composing one ecosystem within the body, requiring similar, limited resources. Furthermore, both strains secrete intercellular signals that alter the development of the cancerous mass and are likely linked through gap junctions that allow for tightly coordinated growth. Thus, the relationship between the two strains fits into an ecological framework and can be appropriately conceptualized with a pre-existing, well-understood ecological model.

**Objective:** We examine the spread of resistance by characterizing the nature of the ecological interaction between populations of resistant and susceptible breast cancer cells.

**Methods:** Using in-vitro data on cell growth, we borrow the Generalized Lotka-Volterra ecological model to infer the type of ecological interaction that occurs between populations of resistant and sensitive cells. In particular, we use Bayesian approach to fit single culture cell populations to infer density-dependent growth parameters (growth rate, carrying capacity) and a Generalized Lotka-Volterra model to understand how susceptible and resistant cocultures populations may be depressing or supporting growth of the other.

Our hypotheses for this interaction are: (1) Exploitative competition, by which susceptible and resistant cells compete indirectly for shared resources. With limited resources, this is the interaction we expect. (2) Interference competition, by which susceptible and resistant cells compete directly by depleting the others' resources. (3) Mutualism or commensalism, in which susceptible and resistant cells support each others growth. The communication via gap junctions also provides this.

**Results & Implications:** We find that it is important to control for the underlying effect of competition (due to constrained resources) between the two populations before inferring the nature of the biological interactions. We also find a net interaction between the susceptible and resistant cancer strains, demonstrating that there are ecological dynamics to cancer resistance.

While the biomedical community's understanding of the evolution of cancer via the incidence of mutations has dramatically improved in recent years, this literature does not explain how the resistant strain becomes dominant once it has developed. These population dynamics are particularly important to understand because it informs how the medical community develops new therapeutic regimens that decrease the incidence of resistance.

# A new lattice-gas cellular automaton model explains plasticity of breast cancer invasion

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Keywords: Cellular automaton, cancer cell invasion, cell adhesion, cell jamming

## Abstract

Plasticity of cancer invasion and metastasis depends on the ability of cancer cells to switch between collective invasion modes and single cell dissemination, under the control of cadherin-mediated cell-cell junctions [1]. E-cadherin is considered a tumor suppressor, the downregulation of which causes single-cell scattering in 2D environments. In clinical samples, however, E-cadherin expressing and deficient tumors both invade collectively and metastasize equally, implicating additional mechanisms controlling cell-cell cooperation and dissemination [2].

Using a lattice-gas cellular automaton model [3, 4] incorporating E-cadherin mediated cell-cell adhesion and physical confinement by the extracellular matrix (ECM), we identify cell jamming by 3D tissue boundaries as the dominant physical mechanism which supports collective invasion irrespective of the composition and stability of cell-cell junctions. In particular, we predict that downregulation of E-cadherin only allows single cell escape under conditions of locally high ECM porosity. Model predictions are validated in spatially defined organotypic culture and using intravital microscopy in breast cancer in mice. Our findings reveal that steric hinderance by 3D tissue can substitute for cadherin-dependent cell-cell cooperation and dictates cell jamming and unjamming in complex environments.

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## Dermal Lymphatic Capillaries Do Not Obey Murray's Law

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Understanding lymphatic development is clinically relevant in applications from embryonic viability, to chronic inflammation, to cancer metastasis. We specifically address the branching of developing lymphatic capillaries, and the flow of lymph through these vessels. Murray's Law is a general branching rule upheld in diverse circulatory systems including leaf venation, sponge canals, and various human organs. While branching in arterial development is understood to consistently follow Murray's Law, we have found that an optimization law for lymphatic vessels follows a different pattern. Here, the daughter vessels are smaller relative to the parent than would be predicted by the hypothesized radius-cubed law. By implementing a computational model using the immersed boundary method, we can examine the extent to which features other than transport cost are optimized in this geometry. This suggests an alternate hypothesis for optimization of a different feature of the lymphatic system, such as enhancing fluid mixing, fluid exchange, or immune cell transport, rather than minimizing fluid transport cost.

*keywords:* lymphatic development, computational fluid dynamics, branching structure, Murray's Law

## Reinforcement learning for the control of bacterial populations in bioreactors

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Multi-species bacterial communities are widespread in natural ecosystems. Engineered synthetic communities have shown increased productivity over single strains and allow for the reduction of metabolic load by compartmentalising bioprocesses between multiple sub-populations. Despite these benefits, co-cultures are rarely used in practice because control over the constituent species of an assembled community has proven challenging. Here we demonstrate, *in silico*, the efficacy of approaches from artificial intelligence – reinforcement learning – in the control of co-cultures within continuous bioreactors. We first develop a mathematical model of bacterial communities within a chemostat that incorporates generalised Lotka-Volterra interactions. We then show that reinforcement learning agents can learn to maintain multiple species of cells in a variety of chemostat systems, with different dynamical properties, subject to competition for nutrients and other competitive interactions. Reinforcement learning was also shown to have the ability to maintain populations within more selective bounds, which is important for optimising the productivity of reactions taking place in co-cultures. Additionally, our approach was shown to generalise to systems of three populations and to be able to cope with random initial conditions. Three species systems represent a level of complexity that has not yet been tackled by more traditional control theory approaches. As advances in synthetic biology increase the complexity of the cellular systems we can build, the control of complex co-cultures will become ever more important. Data-driven approaches such as reinforcement learning will enable greater optimisation of environments for synthetic biology.

## Modeling zebrafish metabolism

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Zebrafish is a popular modeling organism for studying vertebrate development, immune response and metabolism. Experimental metabolic studies can be aided by modelling efforts. Metabolic modeling can be done using mathematical reconstructions of the metabolic network of zebrafish. Such a reconstruction lists the substrates and products of all biochemical reactions that occur in zebrafish. Modeling techniques such as flux-balance analysis can be used to predict metabolic flux distributions that optimize, for example, the turn-over of food into biomass. The only available genome-scale reconstruction of zebrafish metabolism is ZebraGEM (Bekaert, PLOS ONE 2012). Here we present ZebraGEM 2.0, an updated and validated version of ZebraGEM.

A new feature of ZebraGEM 2.0 are the gene-protein-reactions associations (GPRs) that are required to integrate genetic data with the metabolic model. To demonstrate the utility of these GPRs we performed an *in silico* genetic screening for knock-outs of metabolic genes, and validated the results against published *in vivo* genetic knockout and knockdown screenings. Among the single-knockout simulations we identified 74 essential genes, whose knock-out stopped growth completely. Among these, 11 genes are known to have an abnormal knock-out or knock-down phenotype *in vivo*, and 41 have human homologs associated with metabolic diseases.

Another feature added to ZebraGEM 2.0 was the oxidative phosphorylation pathway. The oxidative phosphorylation pathway was validated by comparing with published experiments in which key components of the oxidative phosphorylation pathway were pharmacologically inhibited. Further validation showed that the updated model performs better than the original model on a predetermined list of metabolic functions. We also determined a minimal feed composition. To test the utility of ZebraGEM2.0 for obtaining new results, we integrated gene expression data from control and *Mycobacterium marinum*-infected zebrafish larvae. The resulting model predicts impeded growth and altered histidine metabolism in the infected larvae. We are currently exploring the use of ZebraGEM2.0 for follow-up studies, in particular the effect of infection state on the metabolism and motility of macrophages.

## Distinguishing Between Evolutionary Processes in Cancer Drug Resistance

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The acquisition of resistance limits the effectiveness of many cancer therapies. These include oncogene targeting therapies. This resistance could theoretically be acquired through simple selection of pre-treatment resistant clones, gradual Darwinian evolution or developmental reprogramming, or a mixture of any three. These scenarios provide unique opportunities to interfere with the evolution of resistance, either by targeting resistance intermediates in gradual Darwinian evolution or interfering with the molecular processes involved in developmental reprogramming. To determine the relative roles of these processes we developed resistance to ALK inhibitors in the EML4-ALK lung cancer line H31322. By using colony size as a proxy for fitness (and therefore resistance) and comparing this to a spatial cellular automata model we were able to rule out the possibility of simple selection. We are currently using lineage tracing and branching process models to determine if a single lineage gradually reprograms to a higher fitness state or is subject to multiple selective sweeps, as in Darwinian evolution.

## Forecasting elections using compartmental models of infection

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Election forecasting involves polling likely voters, making assumptions about voter turnout, and accounting for various features such as region demographics and voting history. While political elections in the United States are decided at the state level, errors in forecasting are correlated between states. With the goal of better understanding the forecasting process and exploring how states influence each other, we develop a simple data-driven framework for forecasting U.S. elections from the perspective of dynamical systems. Borrowing ideas from epidemiology, we treat Democrat and Republican voting inclinations as contagions spreading in the year leading up to the election. The parameters in our compartmental model are based on public polling data, and we forecast gubernatorial, senatorial, and presidential elections at the state level. Our results for the 2012 and 2016 U.S. races are largely in agreement with those of popular pollsters, and we use our model to explore how subjective choices about how to include uncertainty impact our forecasts. We conclude by comparing our forecasts for the senatorial and gubernatorial races in the U.S. midterm elections of 6 November 2018 with those of popular pollsters.

# Impact of mitochondrial exchanges on calcium wave propagation in astrocytes

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A growing body of experimental evidence points to the possible remodelling of intracellular calcium ( $\text{Ca}^{2+}$ ) signalling in neurons and astrocytes during Alzheimer's disease (AD).<sup>1,2</sup> Although the role played by  $\text{Ca}^{2+}$  in AD is still unclear, this signalling pathway is a promising avenue to explore.<sup>2,3</sup> Non-neuron-based mechanisms are gradually emerging and stress the need for deeper investigations of astrocyte-based pathways.<sup>4</sup> Recently, the combination of imaging techniques of increasing resolution with the synthesis of targeted  $\text{Ca}^{2+}$  sensors has allowed us to gain insight into the spatial organisation of subcellular  $\text{Ca}^{2+}$  signals in astrocytes.<sup>5</sup> These experiments revealed a complex compartmentalisation of  $\text{Ca}^{2+}$  dynamics across the cell and such a diversity is attributed to the heterogeneous spatial distribution of  $\text{Ca}^{2+}$  pools.<sup>6</sup>  $\text{Ca}^{2+}$  signals initiated by synaptic activity in distal regions of the processes, which usually lack large organelles but can be rich in mitochondria, can propagate to the cell body to induce a physiological response.<sup>6</sup> Understanding how local  $\text{Ca}^{2+}$  signals develop, interact and evolve into global signals is crucial because it is likely that perturbation of this mechanism promotes AD. However, few mathematical models for astrocytic  $\text{Ca}^{2+}$  signalling account for mitochondrial dynamics and this compartmentalisation. In this work, we reproduce the spatiotemporal diversity of  $\text{Ca}^{2+}$  signals with a realistic model accounting for the heterogeneous distribution of  $\text{Ca}^{2+}$  pools (ER and mitochondria). More importantly, we show that wave propagation crucially depends on mitochondrial density in confined regions of the cell such as fine processes.

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## Modelling and optimising the growth and clonality of human embryonic stem cell colonies

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Human embryonic stem cells, hESCs, hold great promise for developments in regenerative medicine and are at the forefront of modern biological research due to their ability to differentiate into any type of human adult cell and their potential to self-renew indefinitely through repeated divisions. Clinical applications often rely on homogeneous cell populations originating from a single cell. As part of an interdisciplinary team at Newcastle University, I am working to optimise experiments by modelling the behaviour of hESC colonies using a combination of agent-based and stochastic techniques. Having already extracted parameters of stem cell kinematics, we now focus on colony proliferation and optimising clonality. Using bespoke experiments from our group, we unexpectedly found colony populations to be multimodal, associated with different numbers of founding cells. This can be predicted by considering cell-cell interactions on randomly seeded cells. We have developed a multi-population stochastic exponential model for the proliferation of hESCs which captures our experimental observations and can be used as a predictive tool to achieve the best outcome for homogeneous clonal colony growth from different seeding densities.

## INFERRING COLLECTIVE BEHAVIOUR RULES FROM FIELD DATA

Jack Walton (presenting)<sup>a</sup>, Andrew Baggaley<sup>b</sup>, Andrew Fletcher<sup>c</sup>, Colin Gillespie<sup>d</sup>

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Many of us have been struck by the inherent beauty of animals moving collectively. Starlings gathering at dusk in huge numbers to perform the most mesmerising of ballets, the entire flock moving as if some fluid object. Fish forming tight milling structures in defence against predation. Though we understand the evolutionary benefits offered to individuals by group behaviour, little is understood about how these structures are formed.

Much work has been invested in developing theoretical agent-based models which seek to explain emergent behaviour by interactions at an individual level. However, these models have largely only been verified with comparison to empirical observation at a qualitative level, and a thorough quantitative comparison between data and theory has been lacking.

Here we seek to make a quantitative comparison between data of flocking sheep and theoretical models. We begin by generalising the formulation of the well-known Vicsek model. Our generalised model allows for the inclusion of biological and behavioural variation between individuals. Working in a Bayesian framework, we utilise the probabilistic programming language Stan to implement the Hamiltonian Monte Carlo algorithm (a type of MCMC algorithm) to infer the parameters of our generalised Vicsek model from our dataset. With this we see how the behaviour of individual sheep varies with their spatial position within the flock, and the importance of allowing for biological and behavioural variation in agent-based models.

## Dynamics of a State Dependent Delay Model of the Tryptophan Operon

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An operon is a functioning segment of DNA which controls the synthesis of certain kind of protein. We are interested in the dynamics of the repressible tryptophan operon which can be modelled by a system of delay differential equations. The delays arise due to the time taken for DNA transcription and mRNA translation. If these delays are assumed to be constant, then the system is known to have a unique steady state which may undergo a Hopf bifurcation leading to a stable period orbit as parameters are varied in the system. In this study, we consider a constant transcriptional delay, but consider the translation velocity to be a variable that depends on the concentration of the intermediate protein. This results in a state-dependent translation delay which is implicitly defined by an integral threshold condition. With the state-dependent delay, we find that it is possible for the system to possess up to three co-existing steady states. We study the stability and bifurcations of and from these steady states as parameters are varied using the software package DDEBiftool and find fold bifurcations, bi-stability of steady states and Hopf bifurcations. We also show how to study the periodic orbits arising from the Hopf bifurcations in the presence of implicit delays.

## A multi-model investigation of mechanobiologic effects on cancer metastases in the liver

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**ABSTRACT:** Liver metastases are a significant cause of death in cancer, but the role of liver tissue mechanics on early metastatic seeding and growth is unclear. In this talk, we join a poroviscoelastic (PVE) model and an agent-based model (ABM) to study how the mechanical interactions between tumor cells and the liver parenchyma (normal liver tissue) affect cancer metastatic seeding and growth in large, centimeter-scale liver tissues. We first develop a detailed poroviscoelastic (PVE) model of interstitial flow and tissue mechanics in a single detailed liver lobule. We investigate flow and tissue deformation in the case of an unobstructed lobule, and in the case of partial tumor obstruction. We then use the PVE model results to motivate constitutive relations to study oxygen transport in large, centimeter-scale sections of liver with hundreds of lobules. This model, along with the PVE model, gives rise to constitutive relations for building a large off-lattice agent-based model of liver metastases. By exploring the space of biomechanical parameters for the stress-based apoptosis in the parenchyma and pressure-regulated cycling in tumor cells, we find that the biomechanical interactions (adhesive, repulsive, and elastic forces on short time scales, and plastic reorganization on longer time scales) play a very important role in the tumor cell's seeding and growth within the liver tissue. In some cases, these interactions arrest the growth of existing micrometastases and prevent newly arriving cancer cells from establishing successful metastatic foci.

Topic Areas: SMB 2019 Contributed Talk Abstract for Mathematical Oncology

## Tissue structure accelerates evolution: premalignant sweeps precede neutral expansion

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Recent debate on tumor heterogeneity has largely centered on the presence (or absence) of subclonal selection. While neutral and Darwinian models of tumor evolution have both been shown to recapitulate bulk sequencing data, multi-region sequencing has produced evidence supporting the hypothesis that early Darwinian selection precedes late neutral evolution after malignant transformation. In this series of exciting and often controversial publications on neutral tumor evolution, little attention has been given to the mechanisms behind the Darwinian-neutral evolutionary transition.

Transitioning modes of evolution (Darwinian to neutral) may be the outcome of cellular architecture dictating varied spatial constraints for growth. Using a classic, well-studied passenger-driver mutation model, we systematically alter spatial constraints and cell mixing rates to show how tissue structure influences both functional (driver) and genetic heterogeneity over time. This novel model extension represents biologically realistic scale ( $10^6$  -  $10^7$  cells) in a biologically realistic setting (3-dimensional breast ductal network derived from imaging data) of premalignant growth.

The model helps unify the debate surrounding neutral tumor evolution by clarifying the role of space in the Darwinian to neutral transition and as a cause of patient-specific variability in selection. The branching topology of ductal networks at tumor initiation determines two important evolutionary accelerants: spatial constraints and cellular dispersal. Connectivity is likely highly heterogeneous between patients, leading to variability in cellular dispersal rates between spatially distinct niches within a tumor. Spatially segregated regions (ductal branches) combined with cell dispersal (subject to branching topology) accelerate evolution. Two otherwise identical tumors may realize dramatic differences in fitness depending on constraints imposed by tissue architecture. Surprisingly, spatial structure dictates the emergent mode of evolution (neutral to Darwinian) without a change in cell-specific mutation rate or fitness effects.

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## B. Title and Abstract

Title:

A Model for How a Foraging Animal Might Determine Step Lengths in a Random Walk

Abstract:

Foraging animals frequently follow a random walk. In recent decades, a substantial amount of theoretical work has been reported on the optimum distributions of step lengths in such walks. This often means a power law distribution with an exponent of roughly -2, and with some method of avoiding the mathematical difficulties (i.e., infinities) of such distributions at very long and very short step lengths. Also in recent decades, advances in technologies have allowed a great deal of empirical data to be collected characterizing the behaviors of individual real animals. Such data are typically analyzed and presented in the context of theoretical expectations. Because of the statistical nature of the data, the limited amount of it for any given animal, and the large range of both step lengths and counts, data are often analyzed and presented in terms of log(count) (longest step is #1, next longest, #2, etc.) vs. log(step length). Animals, one can assume, do not know the theoretically ideal distributions and do not necessarily follow them exactly: only approximately, in so far as evolutionary pressure may have resulted in an acceptable balance of cost vs. benefit.

I will present a mathematical model of a mechanism by which an animal's nervous system might make the decisions that generate a particular distribution of step lengths. The core of this model is a Stochastic Sequential Machine (SSM) that realizes a Markov Chain with a particular state and transition structure. This model produces a continuous probability distribution over the range of step lengths from zero to infinity. This distribution can be numerically integrated to give a good approximation to step-length data in the form of a log-log plot of count vs. step length. The parameters of the model can be adjusted to fit a given set of empirical data. The fitted model can then be used to generate synthetic data that can be compared to the original. Such comparisons can provide insight as to how much of the deviation from the theoretical ideal observed in the empirical data is inherent in the animal (or an artifact of the experimental method) and not just the result of the fundamentally nondeterministic nature of the process. I will use data from the literature on two diving marine predators, an ocean sunfish and a blue shark, to illustrate this capability. I will also describe how a SSM can be decomposed into simple deterministic and nondeterministic information processing parts that might correspond to structures in real nervous systems.

## Stress generation, relaxation and size control in restricted tumor growth

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Experiments on tumor spheroids have shown that compression from their mechanical environment can reversibly decrease tumor expansion rates and final sizes; releasing the stress enables the rates and size distributions to return to their free-growth values. Stress release experiments by cutting, slicing, or punch protocols show that nonuniform anisotropic elastic stresses are distributed throughout the tumors. The elastic stresses are maintained by structural proteins and adhesive molecules, and can be actively relaxed due to processes such as turnover/reassembly of structural and adhesion molecules, cell rearrangements, and oriented cell divisions at timescales spanning from minutes to hours. In this talk, we present a new continuum model to investigate how the instantaneous elastic moduli and active stress relaxation, in conjunction with mechanical feedback machinery within cells, regulate the sizes of and stress distributions within growing tumors in the presence of external physical confinement and gradients of growth-promoting chemical fields. We introduce an adaptive reference map that relates the current position with the reference position but adapts to the current position in the Eulerian frame (lab coordinates) via relaxation. The reference map captures the deformation gradient and associated strains induced by volumetric growth. Although the model reduces to fluid models and linear elastic models in several different limit cases when the active relaxation rate is larger than the volumetric growth rate, we show that these rates can actually be comparable by fitting experimental data from two independent studies of different cancer cell lines. Our study provides insight on how the biophysical properties of the tumor and host microenvironment, mechanical feedback control and diffusion-limited differential growth act in concert to regulate spatial patterns of growth, to generate morphological instability and suggests why increased stiffness is a hallmark of malignant tumors.

This work should be in the subject of **Mathematical Oncology**.

## Modeling the effect of glucose availability on tumor cell growth guided by *in vitro* microscopy

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### Introduction:

Tumor cells adapt their metabolic behavior in response to the varying nutrient availability in their microenvironment. This a combined experimental-computational project designed to predict how tumor cell growth is altered as a function of initial glucose concentration and the initial number of tumor cells competing for nutrients.

### Materials and Methods:

Theory: We constructed a family of models based on ordinary differential equations that describe the temporal evolution in the number of living and dead tumor cells due to changes in glucose concentration and initial confluence. The system estimates proliferation, death (due to glucose depletion and/or the bystander effect), and glucose consumption rates. The Akaike Information Criterion (AIC) was used to select the most parsimonious member of the model family. We then employed a subset of the data to calibrate (or train) our model system to identify trends in model parameters as a function of glucose concentration and initial confluence. These parameters, once calibrated, can then be used to predict tumor cell growth for new experiments with new initial conditions in glucose concentration and confluence.

Experimental: 96-well-plates were systematically seeded with BT474 breast cancer cells at different initial confliences (ranging from 10% to 65%) and different glucose concentrations (ranging from 0 mM to 10 mM) before being imaged by an IncuCyte S3 (EssenBioScience, USA). Phase-contrast images were acquired every three hours for 4 days and Cytotox Red (EssenBioScience, USA) was used to identify dead cells. Confluence at each time point was calculated after live cell segmentation via Matlab (The Mathworks, Inc., USA), generating “confluence time courses” used for computational modeling and further analysis.

### Results:

The model yielding the lowest AIC value featured three global parameters (proliferation rate, death rate due to glucose depletion, and consumption rate of glucose) and one parameter (death rate due to bystander effect) allowed to vary individually with varying initial conditions. We estimated the proliferation rate at  $0.095 \pm 0.002 \text{ day}^{-1}$ , the death rate due to glucose depletion at  $0.012 \pm 0.005 \text{ day}^{-1}$ , and the consumption rate of glucose at  $3.96 \pm 0.11 \times 10^{-5} \text{ mM} \cdot \text{cell}^{-1} \cdot \text{day}^{-1}$ . The death rate due to the bystander effect was found to vary with initial conditions and a 2D surface of this parameter as a function of initial glucose level and live cell confluence was determined. The model prediction presented accuracy (defined as the percentage of data points fall within the 95% confidence interval of the predicted tumor cell number time courses) of 85.0% and 57.8% for live and dead cells, respectively.

### Conclusions:

We have presented results related to the measurement and modeling of tumor cell growth as a function of glucose concentration. Given initial conditions the model can be used to predict tumor cell growth with high accuracy.

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## B. Title and Abstract

Prenatal alcohol exposure in American Indian and Caucasian mothers in the US Northern Plains  
Background

Prenatal alcohol exposure (PAE) is associated with poor pregnancy outcomes. The Safe Passage Study was a longitudinal prospective cohort study designed to investigate the association between PAE and sudden infant death syndrome and stillbirth. A modified Timeline Followback interview was implemented to collect PAE information from ~5,000 women in the Northern Plains of US throughout pregnancy. The participants included a unique mix of rural and American Indian (AI) populations, who were believed to have high prenatal exposure to alcohol.

### Methods

The prevalence of alcohol consumption was compared between AI and Caucasian mothers during pregnancy. Adjusted odds ratios (AOR) of drinking or binging were calculated for race from logistic regression or Bayesian logistic regression models after controlling for demographics, reproductive history, mental health, and socioeconomic status. Significant factors others than race associated with PAE were also identified based on AOR.

### Results

In contrast to the common belief, alcohol consumption in AI mothers was less prevalent than that in Caucasian mothers consistently before, during, and after pregnancy ( $p<0.05$ ). Among drinkers, however, AI mothers drank significantly more based on the drinking amount and the rate of binge drinking ( $\geq 4$  standard drinks on an occasion) ( $p<0.05$ ). The total binge episodes were greater in AI mothers around the last menstrual period (LMP) and during the first trimester (T1) ( $p<0.05$ ), but comparable with Caucasian mothers for the remaining pregnancy. AI mothers had greater odds of binging during LMP and T1 but less odds of drinking afterwards (AOR of binging: LMP=1.40, T1=1.35; AOR of drinking T2=0.52, T3=0.10, Post=0.30). Frequent moves significantly associated with PAE for AI mothers while reproductive history and household income had the most significant associations for Caucasian mothers.

### Future directions

We will evaluate ethanol metabolites in meconium as biomarkers for PAE and identify genetic risk factors for PAE and outcomes. Currently, we are following the same cohort of children from the Safe Passage Study to characterize neurodevelopmental and respiratory outcomes as part of the Environmental influences on Child Health Outcomes (ECHO) program.

### Funding

The Prenatal Alcohol in SIDS and Stillbirth Network was supported by the NIAAA, NICHD, and NIDCD of NIH. The ECHO Program is supported by the OD of NIH.

## Simple Walking in 2-dimensional Space: Model and Experiment

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Our research seeks to model the mechanisms of the human gait in both the stable state and unstable conditions. At the current stage, we are focusing on a simple, two-dimensional dynamical system simulating human legs as constrained movable double pendulum. We test the model with human gait data collected at the Biomedical Engineering laboratory. In the future we intend to expand the model into in three dimensional space via mathematical calculation and affirmation using the lab data.

# Ebola: Impact of hospital's admission policy in an overwhelmed scenario

**Mondal Hasan Zahid** and Christopher M. Kribs

Infectious disease outbreaks sometimes overwhelm healthcare facilities. A recent case occurred in West Africa in 2014 when an Ebola virus outbreak overwhelmed facilities in Sierra Leone, Guinea and Liberia. In such scenarios, how many patients can hospitals admit to minimize disease burden? This study considers what type of hospital admission policy during a hypothetical Ebola outbreak can better serve the community, if overcrowding degrades the hospital setting. Our result shows that which policy minimizes loss to the community depends on the initial estimation of the control reproduction number,  $R_0$ . When the outbreak grows extremely fast ( $R_0 \gg 1$ ) it is better (in terms of total disease burden) to stop admitting patients after reaching the carrying capacity because overcrowding in the hospital makes the hospital setting ineffective at containing infection, but when the outbreak grows only a little faster than the system's ability to contain it ( $R_0 \gtrsim 1$ ), it is better to admit patients beyond the carrying capacity because limited overcrowding still reduces infection more in the community. However, when  $R_0$  is no more than a little greater than 1 (for our parameter values, 1.012), both policies result the same because the number of patients never exceeds the maximum capacity.

## Being Post-Punc: Localising Evolutionary Pulses on Phylogenetic Trees

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Trait evolution is frequently understood as a gradual process, where diverging species accumulate differences over the course of millions of years. However, the fossil record contains evidence of short periods of rapid evolution, followed by very long periods of stasis. This mode of evolution is referred to as punctuated evolution. We will present a method for localising the positions (with uncertainties) and statistical properties of these evolutionary pulses using trait measurements from present-day species, as well as the topology of their common evolutionary tree. This is accomplished by finding the maximum possible likelihood attainable for a set of samples, and deterministically iterating over only those pulse position combinations which are near the maximum information entropy. We will then present examples of detected pulsed trait evolution in new and existing datasets of both physical and social traits, and show that pulsed evolution is the likelier explanation in many cases—even under extreme phylogenetic tree transformations (achieved by MCMC) that optimally benefit the alternate gradual evolution hypothesis.

## Modeling cell shape diversity arising from complex Rho GTPase dynamics

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It is well known that cells exhibit a variety of morphologically distinct responses to their environments that manifest in their cell shape. Some protrude uniformly to increase substrate contacts, others are broadly contractile, some polarize to facilitate migration, and yet others exhibit mixtures of these responses. Prior imaging studies have identified a discrete collection of shapes that the majority of cells display and have demonstrated links between those shapes and activity levels of the cytoskeletal regulators Rho GTPases. Here we use a novel computational modeling approach to demonstrate that Rho GTPase signaling dynamics naturally give rise to this diverse but discrete (rather than continuum) set of morphologies. Specifically, the combination of auto-activation and mutually-antagonistic crosstalk between GTPases along with the conservative membrane (un)binding dynamics readily explain at least 6 of the 7 commonly observed morphologies. We further use this methodology to map the entire parameter space of this reaction-diffusion PDE model and show that in appropriate regimes, individual parameter sets give rise to a variety of different morphologies. This provides an explanation for how seemingly similar cells of the same fate derived from the same population can exhibit a diverse array of cell shapes in imaging studies. These results thus demonstrate that Rho GTPases form the core of a cytoskeletal regulatory system governing cell shape, further supporting the picture that they act as a central signaling hub determining how cells respond to their environmental context.

## Development of computational tools in R for an undergraduate mathematical biology and modeling course

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Undergraduate mathematical biology courses introduce students to a wide range of computational and analysis tools that can potentially span broad mathematical fields such as differential equations, linear algebra, computational mathematics, and statistics. This breadth of subject areas can provide both an integrative experience in mathematics, but also presents conceptual challenges in the management of a wide range of topics. For this presentation I describe the development of computational tools using R to support an upper-division post-calculus course in mathematical modeling and biology. Course topics include an introduction to differential equations and their qualitative analysis, model parameter estimation, and stochastic simulation. The audience for this course includes students majoring in other natural sciences, economics, business, or data analytics. The computational tools developed provide students exposure modern data science techniques and tools in R, but are developed with the aim of furthering understanding of topics in mathematical biology and mathematical modeling. I will also describe the impact of such tools on student learning of the course content.

## Integrated Analysis of Gene Regulatory Networks

(Subdiscipline Area: Mathematical Oncology)

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not sufficient room in the schedule for a talk.

A system-wide investigation of a gene regulatory network involves the analysis of a network of the related genes and the corresponding signal pathways. As a dynamic system, the stable states of a gene regulatory network correspond to the observable stages of the underlying biological system, thus an analysis of all stable states can reveal interesting information of the underlying biological system. The usual methods for such an analysis are based on random simulations. Since not every initial state leads to a stable state, trial and error is necessary. Our approach is to divide the whole system, which is usually large and intractable, into smaller subsystems, and solve these tractable subsystems to obtain partial solutions first. Then we can focus on a substantially smaller collection of states, where different methods, including random methods, can be applied more efficiently, and thus permits the analysis of the stable states globally. This approach was applied to study a regulatory network of prostate cancer. The clusters of the stable states characterize cancer cells, statistical analysis of the stable states revealed that several critical genes had distinct expression behaviors in different cancer cells.