2017 Annual Meeting
Mathematics and Health

Abstract Book
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Plenary Talks

Modelling cancer at multiple scales: From simplifications and idealizations to validations and predictions

Mark Chaplain

Monday, July 17, 9:00–10:00, Douglas Ballroom

The past few decades have witnessed enormous advances in our understanding of the molecular basis of cell structure and function. Life scientists and clinicians are now recognising the need to integrate data across a range of spatial and temporal scales (from genes to tissues) in order to fully understand the systems they are studying. As a specific example of a “cellular system” (but one that has gone wrong), cancer is a complicated disease involving many inter-related cellular processes across a number of scales. However, when considering tissue level phenomena, there are three natural, key scales linked to each other which, when considered together, go to make up understanding the process as a whole: the sub-cellular scale, the cellular scale and the tissue scale itself. In this talk, I will present some recent mathematical models of cancer growth and development which focus on different scales—intra-cellular, inter-cellular and tissue, or micro-, meso-, and macro-scales respectively. The results of the models will be compared with experimental data and some indications of how to develop a unified multiscale mathematical model will be discussed.
Winfree prize talk: Examples of Collective Cell Movement in Biology

Philip Maini
Monday, July 17, 1:30–2:30, Douglas Ballroom

In this talk I will review a number of projects on collective cell movement on which I have been working over the past 10 years. The mathematical approaches will vary from coupled systems of partial differential equations to agent-based models and applications will be drawn from a number of areas in developmental biology and cancer, including neural crest cell migration, crypt-villus dynamics and angiogenesis. The talk will aim to highlight the challenges biology provides for mathematics, and will show how mathematics can lead to new insights into biology.
**Dynamical behaviors of nonlinear complex systems determined from the structure of networks**

Atsushi Mochizuki  
*Tuesday, July 18, 9:00–10:00, Douglas Ballroom*

The successes of modern biology have provided many examples of large networks describing the interactions among many species of bio-molecules. However, we have only a limited understanding of the quantitative details of these systems, such as the regulatory functions and parameter values of reaction rates. To overcome this problem, we developed two theoretical frameworks to extract the important aspects of dynamics from network structure alone, without assuming other quantitative details. The first theory, named Linkage Logic, determines a subset of molecules in regulatory networks from which the long-term dynamical behavior of the whole system can be identified/controlled. This subset is determined from the structure of the network as a Feedback Vertex Set. The second theory, named Structural Sensitivity Analysis, determines the sensitivity of responses of the steady state of chemical reaction networks to perturbations of the enzyme amount/activities. The extent of the responses of chemical reaction networks is determined from the network topology through a new characteristic analogous to Euler characteristic of polyhedra. We apply our methods to several biological network systems, and show they are practically useful to analyze behaviors of biological systems.

Further Reading

Modeling the drivers of coral response to climate change: from genes to communities

Marissa Baskett

Wednesday, July 19, 9:00–10:00, Douglas Ballroom

Given global-scale anthropogenic change such as climate change, a challenge for local conservation and natural resource management is how to protect the capacity for a given system to respond to change through a variety of processes, ranging from genetic adaptation to shifts in community composition. Achieving this goal requires an understanding of the drivers of such response capacity. I will present a series of dynamical models that analyze the drivers of response capacity across ecological scales, from genes to populations to communities, in a system particularly threatened by climate change and CO2 emissions: coral reefs. On the genetic level, I will discuss developing results on the potential for evolutionary change to play a role in coral response to ocean acidification and drivers of adaptive capacity. On the population level, I will discuss coral traits and disturbance characteristics that drive the likelihood of persistence under future climate change. On the community level, I will discuss the potential for species diversity and interactions to drive the overall ecological resilience of a coral-dominated state. Under this multispecies perspective of coral reefs as a complex adaptive system, individual species that are particularly vulnerable to climate change on their own can be crucial to community-level persistence. All three models illustrate the utility of parameter and functional sensitivity analyses for testing the logical intuition of different management priorities to protect response capacity to global change.
Angiogenesis, the formation of new blood capillaries from pre-existing vessels, is a hallmark of cancer. Thus far, strategies for reducing tumor angiogenesis have primarily focused on inhibiting pro-angiogenic factors, while less is known about the therapeutic effects of mimicking the actions of angiogenesis inhibitors. Thrombospondin-1 (TSP1) is an important endogenous inhibitor of angiogenesis that has been investigated as an anti-angiogenic agent. TSP1 impedes the growth of new blood vessels in many ways, including crosstalk with potent pro-angiogenic factors such as vascular endothelial growth factor (VEGF). Given the complexity of TSP1 signaling, a predictive systems biology model would provide quantitative understanding of the angiogenic balance in tumor tissue. Therefore, we have developed molecular-detailed models of interactions between TSP1 and VEGF: a model of breast tumor tissue alone and a whole-body pharmacokinetic-pharmacodynamic model representing breast cancer patients.

The models predict the distribution of the angiogenic factors in tumor tissue and throughout the body, providing insight into the angiogenic balance (and its disruption) in cancer. We utilize the model to simulate administration of exogenous TSP1 mimetics, alone and in combination with VEGF-targeting agents. The models predict the ratio of receptor-bound VEGF to receptor-bound TSP1 following treatment, under various tumor microenvironmental conditions. Excitingly, the modeling results may explain the heterogeneous response observed in the clinical trial involving the anti-VEGF agent bevacizumab combined with the TSP1 mimetic ABT-510. Additionally, we identify potential biomarkers that predict the response to this dual-inhibition treatment protocol. In summary, our systems biology modeling provides a quantitative framework to study the effects of anti-angiogenic treatment.
Mathematical modeling plays a key role in forecasting epidemics, and in planning interventions. Two key measures are “big $R$” and “little $r$”, which I will interpret as measuring epidemic “strength” and “speed”. I will discuss how these two quantities are linked by generation-interval distributions, and interpret this link using approximations and “filtered means”. I will talk about measuring the strength and speed of interventions, on the same scale that we measure strength and speed of epidemics, and argue that little $r$ is under-rated? in particular, that there are strong parallels between the interpretation of big $R$ as a measure of how difficult an epidemic is to control, and an analogous interpretation of little $r$. 


Moving through a turbulent environment: Embedding models in real-world data

Mimi Koehl
Thursday, July 20, 1:30–2:30, Douglas Ballroom

When organisms locomote and interact in nature, they must navigate through complex habitats that vary on many spatial scales, and they are buffeted by turbulent wind or water currents and waves that also vary on a range of spatial and temporal scales. We have been using the microscopic larvae of bottom-dwelling marine animals to study how the interaction between the swimming by a microorganism and the turbulent water flow around them determines how they move through the environment. Many bottom-dwelling marine animals release tiny larvae that are dispersed to new sites by ambient water currents. To recruit to new sites on the sea floor, these larvae must leave the water column and land on surfaces in suitable habitats. We are studying the mechanisms larvae use to move through turbulent flow and land on surfaces. Field and laboratory measurements enabled us to quantify the fine-scale, rapidly-changing patterns of water velocity vectors and of chemical cue concentrations near coral reefs and along fouling communities (organisms growing on docks and ships). We also measured the locomotory performance of larvae of reef-dwelling and fouling community animals, and their responses to chemical and mechanical cues. We used these data to design agent-based models of larval behavior. By putting model larvae into our real-world flow and chemical data, which varied on spatial and temporal scales experienced by microscopic larvae, we could explore how different responses by larvae affected their transport into reefs or fouling communities. The most effective strategy for recruitment depends on habitat.
Contributed Sessions

CS1: Cancer Dynamics

Monday, July 17
10:30–12:30
City Creek Room

List of Talks:

• A discrete stochastic model to simulate the multistep transformation to cancer
  Josie Athens

• Multicellular Modelling of Colorectal Cancer
  James Osborne*

• Impact of Exclusion Processes on Angiogenesis Models
  Samara Pillay*, Helen Byrne, Philip Maini

• Clonal dominance in hematopoietic stem cell compartments
  Peter Ashcroft*, Markus G. Manz, and Sebastian Bonhoeffer

• Quantifying skin and melanoma cell interactions
  Catherine Penington*, Parvathi Haridas, Jacqui McGovern, Sean McElwain, Matthew Simpson

• Mathematical modeling reveals the dynamics of plasma cells in multiple myeloma
  Marcel Mohr*, Dirk Hose, Anja Seckinger, Anna Marciniak-Czochra

• Modeling the Role of Hypoxia in Tumor Metastasis Development
  John Metzcar*, Ines Godet, Daniele Gilkes, Paul Macklin

• Mathematical modeling of antibody drug conjugates, ADCs; Tumor size comparison with actual and ideal linkers
  JongHyuk Byun
Josie Athens
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A discrete stochastic model to simulate the multistep transformation to cancer

Abstract:

In multicellular organisms, when cells divide, random mutations occur in the genome. Most of these mutations may be silent or corrected by repairing mechanisms. In some rare cases, a mutation can confer a cell, neoplastic characteristics that accumulate over time until cancer develops.

At a cellular scale, cancers present a set of distinctive hallmarks, including mutations associated with proliferation, apoptosis, genome instability, angiogenesis and metastasis. In a previous paper (Spencer et al., 2004), we proposed a set of ordinary differential equations to model the multistep transformation to cancer; here I present an extension of those ideas but using a discrete model with stochastic events.

The proposed model starts with a relatively small numbers of cells in which three kinds of different mutations may occur, involving either: apoptosis, proliferation or genome instability. Cells then proliferate at discrete times, allowing for mutations to occur until cells cannot sustain growth unless they acquire further mutations associated with angiogenesis and metastasis. As discrete events are stochastic, simulations were replicated 100 times, and the mean values for the number of each mutant were estimated.

Although the dynamics for single mutants depends on the first mutation, the dynamics for the tumour cells is independent of the starting mutation.

The proposed model is relatively simple and can be extended to simulate other events, besides cancer.

References:

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B. Title And Abstract

Title: Multicellular Modelling of Colorectal Cancer

Abstract: Colorectal cancer (CRC) is one of the major causes of death in the developed world. CRC arises when the cells lining the gut (which consist of millions of distinct test tube shape domains called crypts) undergo a string of mutations causing them to no longer respond to the usual control mechanisms. Possible treatments attempt to restore these control mechanisms by providing drugs, which change how cells respond to stimuli.

Much mathematical and computational modelling has been undertaken in order to try to understand how crypts develop and how things go wrong under disease. We have developed a framework, which combines mechanical models of cell interactions with detailed representations of the subcellular machinery. The framework allows the specification of arbitrary subcellular networks in the Systems Biology Markup Language (SBML) within a selection of multicellular representations of the crypt. Allowing the multiscale models to be simulated and the effects of mutations in individual cells, and their influence on the crypt, to be investigated.

In this talk we present the coupled multicellular models underlying the framework; discuss its implementation; and present example applications of the framework, including the inclusion of mutations in the system and their effect on the Crypt.
SMB 2017 Contributed Talk Abstract

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B. Title and Abstract
Impact of Exclusion Processes on Angiogenesis Models

Angiogenesis is the process by which new blood vessels develop from existing vasculature, and is important in pathological conditions, such as cancer. Tumor angiogenesis has been modeled phenomenologically using the well-known snail-trail approach. We use an alternative methodology, utilizing an agent-based approach to model the behavior of individual endothelial cells during angiogenesis. We incorporate crowding effects through volume exclusion, motility of cells through biased random walks, and include birth and death-like processes to represent sprout formation and anastomosis. We use the transition probabilities associated with the discrete model and a mean-field approximation to systematically derive a series of partial differential equation (PDE) descriptions of collective cell behavior that vary in complexity depending on the extent of volume exclusion incorporated on the microscale. This general framework generates non-linear PDEs that impose physically realistic density restrictions, and are structurally different from existing snail-trail models which implicitly view cells as point particles. We compare solutions to our PDEs and a well-known snail-trail model to discrete simulation results to determine conditions under which it is necessary to account for cell volume in the continuum models. We find that for a single-species exclusion process, once cell density exceeds a threshold, the implicit point particle assumption in snail-trail models leads to non-negligible errors. In the case of multi-species exclusion, both model types perform poorly once interaction between the cell species becomes pronounced. In general, snail-trail models perform well when exclusion effects are diminished at the macroscale; in other cases, non-linear models should be used. In future, we aim to distinguish model performance based on network morphology. This may impact drug development strategies based on PDE models.
SMB 2017 Contributed Talk Abstract

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B. Title and Abstract
Title: Clonal dominance in hematopoietic stem cell compartments.

Abstract:
Clonal hematopoiesis — where mature myeloid cells deriving from a single stem cell are over-represented — is detected in at least 10% of people aged 70 and over and represents a major risk factor for overt hematologic malignancies. To quantify how likely this phenomena is, we combine existing quantitative observations with a novel stochastic model of hematopoietic stem cell dynamics. We include migration between stem cell compartments — in mammals these cells reside mostly in the bone marrow, but also transitively passage in small numbers in the blood. We find in mice that cells require a selective advantage, i.e. it can not be a by-chance neutral expansion, if a clone is to be detectable within a lifetime. In humans this prediction is dependent on the number of stem cells, which is frequently debated. Combining our predictions with incidence data establishes a lower bound for the number of hematopoietic stem cells in man. The compartmental nature of our model further captures scenarios of stem cell transplantation in preconditioned and non-preconditioned hosts. Our analyses support existing findings that niche-space saturation decreases the engraftment efficiency of donor cells.
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B. **Title and Abstract**

**Title:** Quantifying skin and melanoma cell interactions

**Abstract:**  Melanoma is the third most common cancer in Australia, and associated with high rates of mortality. Melanoma spreading involves the migration of cancer cells amongst other native skin cells. We explore the interactions between melanoma cells and fibroblast cells by performing a suite of cell barrier assays with one or two types of cells at different ratios, and compare the experimental results to mathematical models. This allows us to investigate the interactions between the two types of cell, and reveals no evidence of interactions other than cell-to-cell contact.
SMB 2017 Contributed Talk Abstract

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B. Title and Abstract
Mathematical modeling reveals the dynamics of plasma cells in multiple myeloma

Plasma cells (PCs) are white blood cells, which represent an essential part of the immune system producing the main fraction of antibodies. After an antigen encounter, a large population of non-proliferative PCs is generated, which enters the bone marrow to reside therein. Interactions with the bone marrow microenvironment, termed the niche, permit PCs to survive for decades. Yet, competition for the niche leads to PC displacement and their concomitant death. In contrast to healthy PCs, malignant PCs proliferate. Their accumulation in the bone marrow characterizes malignant PC diseases. Asymptomatic multiple myeloma (AMM) evolves from monoclonal gammopathy of unknown significance (MGUS). These two disease stages are asymptomatic and delineated solely by surrogates of tumor mass. Disease progression leads to multiple myeloma (MM) involving clinical signs and symptoms such as end organ damages.

The goals are to understand the evolution of malignant PC diseases within an individual patient and to reveal the underlying mechanisms of cancer development. Three main questions are addressed by mathematical modeling. Firstly, how is growth of malignant PCs characterized? Secondly, how fast does progression from asymptomatic stages (AMM, MGUS) to symptomatic myeloma (MM) happen? And thirdly, can a single malignant PC explain the development of myeloma? Or is such initial event rather characterized by a large population of malignant PCs arriving at the bone marrow, thus comparable to healthy PC development induced by an antigen encounter?

To answer these questions, new mathematical models consisting of piecewise-smooth ordinary differential equations are derived, which describe the dynamics of healthy and malignant PCs in the bone marrow and its niche. The models are validated using clinical data of patients with AMM (n=322) and MGUS (n=196), eventually allowing for novel biologically and clinically relevant conclusions.
Title: Modeling the Role of Hypoxia in Tumor Metastasis Development

Abstract: Breast cancer metastases are the leading cause of breast cancer related death. Hypoxia is common in breast cancer, is a negative prognostic factor, and is associated with breast cancer metastases. In this talk, we present data from new immunofluorescent and immunohistochemical stains for hypoxic exposure, which are retained after cells return to normal physiological oxygen conditions. The data are paired with traditional hypoxic markers, blood vessel labels, cell birth and death markers, spatial oxygenation measurements, and tumor size measurements. Based on these data obtained in an orthotopic mouse model, we develop and calibrate an agent-based model of vascularized primary tumor growth. We match this primary site model to a PDE-based metastatic site model, which includes the effects of tissue mechanics, oxygen-driven birth and death, and vascular remodeling. We encapsulate this PDE model into a “metastasis agent”, and network those agents to simulate multi-site metastatic progression. We present preliminary results on metastatic dissemination, compare our results with early in vivo data on hypoxic cell trafficking, and discuss how this system could be used to explore the systemic impact of anti-angiogenic treatments.
SMB 2017 Contributed Talk Abstract

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B. Title:
Mathematical modeling of antibody drug conjugates, ADCs; Tumor size comparison with actual and ideal linkers.

Abstract

Antibody drug conjugates, ADCs, are one of the latest developed chemotherapeutics that treat some types of tumor cells. It consists of monoclonal antibodies, linkers, and potent cytotoxic drugs. Unlike common chemotherapies, ADCs combine selectively with the target at tumor cell surface and potent cytotoxic drug (payload) effectively prevents microtubule polymerization. This magical drug has theoretically perfect but linkers are not stable and payloads release in the circulation before binding the target. It may cause side effect in the body. In this work, we construct an ADCs model that considers both the target of antibodies and the receptor (tubulin) of the cytotoxic payloads and then presents the comparison with tumor size prohibition effects according to linker stabilities after estimating parameters and sustaining half-life. This research will propose the effect and limitation of upcoming new ADCs drugs about linker improving.

Key words: Pharmacokinetics and pharmacodynamics (PK/PD), signal distribution model (SDM), Monoclonal antibodies, Antibody drug conjugates, Target-mediated drug disposition, Mathematical ADCs model, AUC, half-life, linker stability
CS2: Dynamical Systems
Monday, July 17
10:30–12:30
Bonneville Room

List of Talks:

- **Threshold dynamics of a cholera epidemic model in a spatiotemporally heterogeneous environment**
  Xueying Wang*, Xiaoqiang Zhao, Jin Wang

- **Modeling and Estimation of Population Dynamics for the maculata Apple Snail**
  Lihong Zhao* and Karyn L. Sutton

- **The Importance of Synchrony in Mass Drug Administration**
  Daozhou Gao*, Thomas M. Lietman, Chao-Ping Dong, Travis C. Porco

- **The Binding and Unbinding Dynamics of Tropomyosin and Actin**
  Adelle C.F. Coster*, Miro Janco, Till Boecking

- **Modeling the Complex Role of Testosterone in Ovulation**
  Erica J. Graham*, James F. Selgrade

- **Probabilistic modeling of reprogramming to induced pluripotent stem cells**
  Lin L. Liu*, Justin Brumbaugh, Ori Bar-Nur, Zachary Smith, Matthias Stadtfeld, Alexander Meissner, Konrad Hochedlinge, Franziska Michor
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Presenter: Xueying Wang

B. Title And Abstract

Title: Threshold dynamics of a cholera epidemic model in a spatiotemporally heterogeneous environment

Abstract: The transmission of cholera, a water- and food-borne intestinal infection, involves complex interactions among human hosts, pathogens, and the environment, and is impacted by the spatial variation and seasonal fluctuation. In this paper, we propose a new deterministic model to investigate the spatiotemporal dynamics of cholera transmission. The model employs a reaction-convection-diffusion system to represent the spatial movement of the hosts and pathogens, and incorporates time-periodic parameters to describe the seasonality of the disease transmission and bacterial growth rates. Using the theory of principle eigenvalues, we define and analyze the basic reproduction number of this model, based on which we establish the threshold type results for cholera transmission in a spatiotemporally heterogeneous environment.
Modeling and Estimation of Population Dynamics for the *maculata* Apple Snail

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Abstract

*Pomacea maculata* is an amphibious snail species that began invading freshwater wetlands and waterways along the northern Gulf of Mexico coast ten years ago, and potentially threatens local agriculture and ecosystems. Their vital rates have largely been unquantified. Laboratory raised *P. maculata* were followed from hatchling to adult over the course of three years. Our data suggests sex-dependent, size-dependent and temperature-dependent differences in growth. We discuss the calibration of a size-structured mathematical model of *P. maculata*'s population dynamics based on our experimental studies. Using this model as a tool to make population projections under different environmental scenarios, we present simulation studies and as a means to explore competing hypotheses regarding this species’ natural history. We demonstrate that this model can be used to quantify the local population size, and make population projections under various proposed management scenarios.
SMB 2017 Contributed Talk Abstract

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B. Title and Abstract
Title: The Importance of Synchrony in Mass Drug Administration
Abstract: Mass drug administration (MDA), a strategy in which all individuals in a population are subject to treatment without individual diagnosis, has been recommended by the World Health Organization for controlling and eliminating several neglected tropical diseases. In this talk, we will present some results arising from mass treatment of trachoma with azithromycin. We compare three typical drug distribution strategies (regardless of health status): constant treatment, impulsive synchronized MDA, and impulsive non-synchronized treatment. We show that synchronized and constant strategies are respectively the most and least effective treatments in disease control. Elimination through synchronized treatment is always possible when adequate drug efficacy and coverage is fulfilled and sustained. This is joint work with Thomas M. Lietman, Chao-Ping Dong, and Travis C. Porco.
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B. Title and Abstract

The Binding and Unbinding Dynamics of Tropomyosin and Actin

The actin cytoskeleton plays a critical role in most cellular processes, controlling and regulating many different cellular properties and functions such as shape, adhesion and migration, cytokinesis, membrane function and intracellular transport. The intracellular localisation of the actin, the filament organisation, as well as the dynamics and interaction of actin with different tropomyosin isoforms is thought to be the key determinant of difference in behaviour and function.

In vitro fluorescence imaging has developed as an important tool in the observation of the kinetics of the polymerisation of actin filaments and interactions with actin-binding proteins. However, much of this activity occurs well below the resolution of imaging systems. We have developed mathematical methods to identify different behaviour, extract kinetic parameters and determine association constants in an unbiased fashion, and to create a mathematical model of actin cytoskeleton function.

The actin filament has two edges along which the tropomyosin can bind. The mathematical model considers the actin filament as two one-dimensional lattices along which the tropomyosin can bind and unbind. The model encodes the different ways in which the tropomyosin binds, both in the presence and absence of other bound tropomyosin, and how it unbinds from the actin. Analysis of the dynamics is used to tease apart the behaviour observed in the experimental studies and add new insight into the mechanism of actin decoration.
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B. Title and Abstract
Title: “Modeling the Complex Role of Testosterone in Ovulation”
Abstract: Polycystic ovary syndrome (PCOS) is a common cause of infertility of unknown etiology. Often characterized by ovulatory dysfunction due to increased ovarian androgen production, PCOS is also frequently associated with insulin resistance and insulin-mediated androgen overproduction. However, the precise role of testosterone and other androgens in cycle disruption remains unclear. We discuss a mathematical model of the ovulatory cycle, taking into account the known and hypothesized roles of testosterone under physiological circumstances, and we explore ovulatory dysfunction under pathological insulin-dependent changes in testosterone. Model results suggest that varied signal responses of ovarian follicles can alter the extent of ovulatory dysfunction. The model also provides insight into the various PCOS phenotypes and the severity of ovulatory dysfunction.
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B. Title and Abstract
Title: Probabilistic modeling of reprogramming to induced pluripotent stem cells
Abstract: Reprogramming of somatic cells to induced pluripotent stem cells (iPSCs) is typically an inefficient and asynchronous process. A variety of technological efforts have been made to accelerate and/or synchronize this process. To define a unified framework to study and compare the dynamics of reprogramming under different conditions, we developed an in silico analysis platform based on mathematical modeling. Our approach takes into account the variability in experimental results stemming from probabilistic growth and death of cells and potentially heterogeneous reprogramming rates. We suggest that reprogramming driven by the Yamanaka factors alone is a more heterogeneous process, possibly due to cell-specific reprogramming rates, which could be homogenized by the addition of additional factors. We validated our approach using publicly available reprogramming datasets, including data on early reprogramming dynamics as well as cell count data, and thus we demonstrated the general utility and predictive power of our methodology for investigating reprogramming and other cell fate change systems.
CS3: Computational Biology I
Monday, July 17
3:00–5:30
City Creek Room

List of Talks:

• *A mathematical model of cartilage regeneration after cell therapy mediated by growth factors*
  Kelly Campbell*, Shailesh Naire, Jan Herman Kuiper

• *Modeling the dynamics of heterogeneity in response to chemotherapy*
  Heyrim Cho*, Doron Levy

• *Multiscale model of Hepatitis C Virus infection by PDE could be reduced into simple ODE model*
  Kousaku Kitagawa*, Shinji Nakaoka, Yusuke Asai, Shingo Iwami

• *Data mining of metabolic interactions in a gut microbial community induced by viral infection*
  Shinji Nakaoka*, Kei Sato

• *Influence of Driving Mechanics on Bacterial Motility in Confined Environments*
  John LaGrone*, Lisa Fauci, Ricard Cortez

• *Elimination for systems of nonlinear ODEs arising in biology*
  Gleb Pogudin*, Alexey Ovchinnikov

• *Computationally Efficient Approximations for the Equilibrium Probability Distribution of the Chemical Master Equation*
  Brandon Reid*

• *The Modelling and Computation of Multi-Mode Biological Data of Mental Disorder*
  Lin Wan*
A mathematical model of cartilage regeneration after cell therapy mediated by growth factors

Autologous Chondrocyte Implantation (ACI) is the most commonly used cell-based therapy for treating chondral defects in joints, such as the knee. The procedure begins by inserting chondrocytes, previously expanded in culture, into the defect region. The chondrocytes initiate the healing process by proliferating and depositing extracellular matrix (ECM), which allows them to further migrate in the defect until it is completely filled with new cartilage. Mesenchymal stem cells (MSCs) can be used instead of chondrocytes in this procedure with very similar long term results. The main differences are at early times because MSCs must first differentiate into chondrocytes before cartilage is formed.

To enable better understanding of this repair process, we present a mathematical model of cartilage regeneration after cell therapy. The key mechanisms involved in the regeneration process were simulated by modelling cell proliferation, migration and differentiation, nutrient diffusion and ECM synthesis at the defect site, both spatially and temporally. In addition, we modelled the interaction between MSCs and chondrocytes by including growth factors which are produced by these cells and thought to influence each other's proliferation and differentiation rates. An example is Fibroblast Growth Factor 1, produced by MSCs and stimulating chondrocyte proliferation.

Our results show that matrix formation was enhanced at early times under these conditions when compared with simulations not considering the effects of growth factors, reinforcing the importance of cell-to-cell interaction in the healing process. The co-implantation of MSCs and chondrocytes into chondral defects impacted the overall healing time. Our results indicate the implantation of any combination of MSCs and chondrocytes improved the rate of healing within the first year when compared with chondrocyte only or MSC only implantation, potentially allowing the patient to become mobile sooner after surgery. The model presented enables us to better understand articular cartilage regeneration giving us invaluable insight into potentially important advances in cell-based therapies.
A. Authors
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Doron Levy
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B. Title And Abstract

Title: **Modeling the dynamics of heterogeneity in response to chemotherapy**

Abstract: We develop a model of the dynamics of drug resistance in a solid tumor based on the work of Lorz et al. Bull. Math. Bio. 77:1-22, 2015. The quantities we follow depend on a phenotype variable that corresponds to the level of drug resistance. By considering a growth term that takes into account the sensitivity of resistance level to high drug dosage, we show that increased drug concentrations are correlated with delayed relapse and higher level of resistant traits. We further show that an on-off drug infusion also selects for more resistant traits when compared with a continuous drug infusion of identical total drug concentrations. In addition, the permeability of the resource and drug and is limited by the cell concentration in our model that impacts the resistance level. Under certain conditions, our model predicts the emergence of a heterogeneous tumor in which cancer cells of different resistance levels coexist in different areas in space. Finally, we incorporate a cell growth model and study the impact of resistance on tumor growth and success of chemotherapy.
Authors
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Title
Multiscale model of Hepatitis C Virus infection by PDE could be reduced into simple ODE model

Abstract
Hepatitis C Virus (HCV) infection is still a world-wide health problem, although the antiviral therapy has been incredibly improved so far. Multiscale model using partial differential equation (PDE) could describe both intercellular and intracellular dynamics of HCV infection. However, mathematical analysis of a PDE model is not easy in general, and its numerical simulation is time consuming compared with ordinary differential equation (ODE) models. In this research, we transformed the PDE model, which is previously proposed by J. Guedj et al., in PNAS (2013), into the ODE model without any mathematical assumptions. Interestingly, we found our ODE model perfectly reproduce the original PDE numerical simulations, although an approximate solution derived by Guedj et al. might be able to reproduce the PDE simulations under specific conditions. Since numerical cost is considerably low, our ODE model obtained from the PDE model is useful for clinical data analysis, especially for parameter estimations.
Authors
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Title
Data mining of metabolic interactions in a gut microbial community induced by viral infection

Abstract
Reduced species diversity, known as dysbiosis, has been observed among gut or skin microbiota during the onset of chronic inflammatory disease. Enrichment of pathogenic bacteria has also been observed when individuals are infected with viral or pathogenic bacteria. These findings indicate the importance of relationship between species composition change and sustained chronic inflammation.

In this presentation, we introduce our recent progress on mining metagenomic alternations induced by viral infection observed in human or animal infection models. We developed a bioinformatics pipeline to calculate bacterial species composition from 16S amplicon sequencing data, target sequencing of variable regions in the 16S rRNA DNA region. To extract potential metabolic activity of a given microbiota, several existing databases for bacterial genome and metabolism were used to infer gene contents, followed by metabolic network inference. Based on these data-mining procedures, we obtained a list of metabolic candidates that is expected to be associated with elevation of immune responses, or invasion of pathogenic bacterial species. Some theoretical consideration will be discussed why a particular type of bacterial species are preferred in an inflammatory state.
B.

Influence of Driving Mechanics on Bacterial Motility in Confined Environments

We are interested in the propulsion dynamics of bacteria in porous materials such as soil, specifically with applications related to environmental remediation. In order to characterize bacterial swimming in confined environments, we present a computational model of flagellar driven bacteria and their hydrodynamic interactions. We construct an elastic body and flagella using networks of springs and present two models of a flagellar motor: one based on placing torques and the base of each flagella and the second by creating a ratcheting system of springs. The interaction with the surrounding fluid is modeled using the method of regularized Stokeslets.

By placing the modeled bacteria in narrow tubes, we investigate how the flagellar driving and confinement influence the swimming properties. We have observed self centering behavior in the case of the torque driven flagella, but not with the ratcheting system. Additionally, we observe increased swimming speed in tubes of smaller radii and are investigating how the confinement influences the tumbling dynamics of the swimming bacteria.
A. Authors

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B. Title and Abstract

Title: Elimination for systems of nonlinear ODEs arising in biology.

Abstract: The following problems arise in modelling biological processes using ordinary differential (or difference) equations:

1. Eliminate (if possible) un-observable unknowns and obtain equations in the rest of the unknowns.

2. Express the parameters of the system (if possible) in terms of the observable unknowns and their derivatives.

We will discuss recent algorithms for solving these problems and illustrate them using systems arising in biological modelling (for example, for HIV-models).
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B. Title and Abstract

Computationally Efficient Approximations for the Equilibrium Probability Distribution of the Chemical Master Equation

In macroscopic models, chemical reactions are usually analyzed with continuous variables and deterministic ordinary differential equations where the inputs are the concentrations of the species present, the reaction rates between various species, etc. However, on the microscopic level, the discrete nature of the reactants comes into play. In such cases, chemical reactions are frequently modeled as Markov processes. Though we must consider the discrete nature of the molecules at the microscopic level, we often deal with enough molecules that it is computationally very expensive to model these processes. Depending on the size of the chemical system, solving for the equilibrium probabilities of the system using a matrix representing the chemical master equation can be extremely computationally costly. We are confronted with a conundrum: microscopic chemical systems are often too small to be modeled deterministically and too large to be solved directly without great computing power. Even Monte-Carlo methods can become quite computationally expensive, especially for systems of high dimension. Therefore, we seek ways to approximate the equilibrium distribution more efficiently. To this end, we explore a method of quickly identifying possible modes of the stationary distribution of the chemical master equation and examining the relative probabilities of the regions surrounding the distribution’s modes through an analysis of the propensity functions of each chemical reaction in the system.
SMB 2017 Contributed Talk Abstract

A. Authors

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B. Title And Abstract

Title: The Modelling and Computation of Multi-Mode Biological Data of Mental Disorder

Abstract: The accumulation of multi-mode data (e.g. genetics, gene expression, imaging, symptoms, and environments data) in brain science provides an essential opportunity for researchers to study brain functions and mechanisms of mental disorder in a comprehensive way. At the same time, it raises new questions and great challenges for researchers, in particular for those in the field of computational and systems biology. In response, we have been conducting a series of studies in the modeling, computation, and synthesis of multi-mode data by emphasizing the key characteristics of the data that include high-dimensionality, multi-mode/multi-scale, and heterogeneity. In this talk, I will report our recent results on (1) subtyping schizophrenia with the bipartite graph community detection method and (2) identifying and tracking of spatial-temporal brain development gene networks. The challenges on integrating multi-mode data will also be addressed.
List of Talks:

- *Modeling the Excess Cell Surface Stored in a Complex Morphology of Bleb-Like Protrusions*
  Jia Zhao*

- *Mitochondria are essential to the intracellular calcium response to shear stress in a mathematical model of vascular endothelial cells*
  Richard Buckalew*, Arash Moshkforoush, Christopher Scheitlin, Nikolaos Tsoukas

- *A Mathematical Model of Translation Regulation by the Integrated Stress Response*
  Laura F Strube*, Frederick R Adler

- *Effect of Plexin-D1 and Notch Signaling in Retinal Sprouting Angiogenesis*
  Colette Calmelet*, Aasakiran Madamanchi, Mary Zutter

- *TGF-beta regulated chondrogenesis for tissue engineering of articular cartilage*
  Mike Chen*, Sarah Waters, Jonathan Whiteley, Colin Please, Helen Byrne

- *Hyperplastic vs. Hypertrophic Expansion: the More or the Merrier*
  Katrina Johnson*, Fred Adler

- *Dynamic compartmentalization and mechanical forces in cellular functions and disease*
  Tatiana T. Marquez-Lago*
SMB 2017 Contributed Talk Abstract

**Speaker:** Jia Zhao, Department of Mathematics, University of North Carolina at Chapel Hill; Email: zhaojia@email.unc.edu

**Title:** Modeling the Excess Cell Surface Stored in a Complex Morphology of Bleb-Like Protrusions

**Abstract:** Cells transition from spread to rounded morphologies in diverse physiological contexts including mitosis and mesenchymal-to-amoeboid transitions. When these drastic shape changes occur rapidly, cell volume and surface area are approximately conserved. Consequently, the rounded cells are suddenly presented with a several-fold excess of cell surface whose area far exceeds that of a smooth sphere enclosing the cell volume. This excess is stored in a population of bleb-like protrusions (BLiPs), whose size distribution is shown by electron micrographs to be skewed. We introduce three complementary models of rounded cell morphologies with a prescribed excess surface area. The models form a general framework for future studies of cell morphological dynamics in a variety of biological contexts.
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B Title & Abstract

Mitochondria are essential to the intracellular calcium response to shear stress in a mathematical model of vascular endothelial cells.

Fluid shear stress applied to endothelial cells (ECs) causes a signal cascade starting at the plasma membrane that results in the generation of Inositol triphosphate (IP$_3$) within the cell. This causes IP$_3$R calcium channels on the membrane of the endoplasmic reticulum (ER) to release a large amount of Ca$^{2+}$ from the ER into the cytosol, causing a transient peak. If the cell remains stimulated, this initial peak is followed by indefinitely many oscillatory [Ca$^{2+}$]$_i$ peaks.

The coevolution of experimental results and mathematical models has been a key driver in the rapid increase in understanding of these oscillations over the last 20 years. It is presently accepted that the mitochondria act as a buffer to modulate the [Ca$^{2+}$]$_i$ dynamics through their close interaction with the ER. However, recent experimental results by Scheitlin et al indicate that mitochondria play a more fundamental role in the generation and maintenance of [Ca$^{2+}$]$_i$ oscillations.

We present a detailed model of the intracellular Ca$^{2+}$ dynamics in sheared ECs that includes mitochondria as well as microdomains. Microdomains are small volumes of cytosol that exist in regions of close apposition between the ER and mitochondria, and appear in conjunction with mitochondrial associated membranes (MAMs).

We show that the MAMs and corresponding microdomains are essential for producing and maintaining the physiological [Ca$^{2+}$]$_i$ oscillatory response to shear stress in the model, and can sustain oscillations with or without flux from the extracellular space. Further, we show that the proportions of microdomain-facing IP$_3$R, mitochondrial uniporter (MCU), mitochondrial Na$^+$/Ca$^{2+}$ exchanger (mNCX), and sarco/endooplasmic reticulum Ca$^{2+}$ ATPase (SERCA) channels act as critical controllers of oscillatory behavior.
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2 Title and Abstract

A Mathematical Model of Translation Regulation by the Integrated Stress Response

The Integrated Stress Response (ISR) is a protective mechanism that is activated in response to a wide variety of intracellular stresses. Cells use the ISR to temporarily attenuate canonical translation while simultaneously upregulating the translation of stress response genes via a non-canonical pathway. The key proteins in this system are the eukaryotic initiation factor eIF2α, its recycler eIF2B, a stress-detecting eIF2α kinase, and the transcription factor ATF4. We describe a non-linear ODE model of ISR-induced translation regulation incorporating stochastically derived reaction rates that describes translation as a function of stress level. We show that the model exhibits three qualitative behaviors corresponding to degree of stress. When stress levels are low, the system acts as a filter and maintains general translation while exhibiting minimal translation of ATF4. Under intermediate levels of stress, the system produces ATF4 protein while reducing general translation. When stress levels are high both general translation and ATF4 translation fail. This model demonstrates that the stochastic mechanism underlying ATF4 translation allows the cell to differentially regulate two translation mechanisms despite their reliance on the same initiation factors.
SMB 2017 Contributed Talk Abstract

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B. Title And Abstract

Effect of Plexin-D1 and Notch Signaling in Retinal Sprouting Angiogenesis

Abstract:
We present a hybrid mathematical model to simulate the morphological and signaling features observed in the postnatal development of the mouse retinal vascular network. We solve numerically a multiscale differential system consisting of two parts: macro and micro; and analyze its solutions for different values of the sensitivity coefficients. These results provide information regarding the mechanism of how VEGF-Notch signaling system directs the formation of morphological features in the retina, including the development of retinal vascularization, plexus density, and plexus irregularity. Additionally, we use this model to predict how crosstalk molecules signal to the VEGF-Notch axis to modulate various vascular phenotypes. We obtain analytical expressions of the differences in the steady-state solutions of a simplified two-cell signaling system. We investigate in particular the stabilizing effect of Plexin-D1 on the VEGF-Notch microsystem. This work provides an insight into the molecular mechanism of retinal sprouting angiogenesis and can help identify potentially synergistic therapeutic approaches.
SMB 2017 Contributed Talk Abstract

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B Title And Abstract

Title: TGF-β regulated chondrogenesis for tissue engineering of articular cartilage

Abstract: The differentiation of mesenchymal stem cells (MSCs) into chondrocytes (native cartilage cells), or chondrogenesis, is a key step in the tissue engineering of articular cartilage, where MSCs are used as seed cells to take advantage of their motility and high proliferation rates. This process is regulated by transforming growth factor-beta (TGF-β), a short-lived cytokine whose effect is prolonged by storage in the extracellular matrix. A motivating in vitro tissue engineering approach involves seeding a population of MSCs in a hydrogel construct, and applying strategies to drive differentiation of the initial cell population. Two common strategies are (1) co-culture the MSCs with chondrocytes, which constitutively produce TGF-β; or (2) add exogenous TGF-β. To investigate these strategies we develop an ODE model of the life-cycle of TGF-β, the dynamics of which are much faster than those of the cell processes. This difference in time-scales is exploited to construct various asymptotic approximations for the concentration of TGF-β, and these match closely with numerical simulations. For strategy (1) we find that full chondrogenesis will be induced if the initial proportion of chondrocytes is above a critical value. Similarly, for strategy (2) there is a critical initial concentration of exogenous TGF-β above which all the MSCs will be driven to differentiate. Finally, we use the model to investigate whether there is an advantage in using a hybrid strategy where exogenous TGF-β is added to a co-culture, as compared to using either strategy (1) or (2) in isolation.
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B. Title and Abstract
Hyperplastic vs. Hypertrophic Expansion: the More or the Merrier 

Abstract
Adipocytes are the primary cell type in adipose tissue and are responsible for limiting the exposure of other tissues to lipid accumulation during the postprandial state and providing energy by releasing lipids during periods of fasting. Adipose tissue expands by increasing the size of adipocytes, hypertrophic expansion, and/or the number of adipocytes, hyperplastic expansion, in response to positive energy imbalance. We developed a size structured model to explore the population dynamics of adipocytes in response to fluctuation in energy storage demands. We use this model to examine the hypothesis that hypertrophy is the short-term response to positive energy imbalance and hyperplasia is an additional response to long-term energy imbalance. This model provides a foundation for studying obesity associated pathologies such as chronic inflammation and insulin resistance.
SMB 2017 Contributed Talk Abstract

Section A

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Section B

Title: Dynamic compartmentalization and mechanical forces in cellular functions and disease

Abstract:

Despite intrinsic and extrinsic sources of stochasticity, spatial segregation and organization of molecules within cells enables activation and repression of transcriptional programs, precise signal transduction, and cell fate decisions. Two relevant mechanisms shown to be involved in cellular precision are mechanical forces and compartmentalization of cell membranes.

In this talk, I will discuss how a combination of cell biology, microscopy and spatio-temporal stochastic modelling and simulation has helped us elucidate the role of dynamic compartmentalization and mechanical forces in key cellular functions. We will discuss examples in asymmetrical inheritance of transcriptional activators, stability of signaling complexes, and vesiculation events along the endocytic and endosomal pathways. Lastly, we will discuss next-generation mathematical modeling and simulation tools relevant to biology and biomedical sciences in the context of specific disease models.
CS5: Evolution and Plant Ecology

Tuesday, July 18
10:30–12:30
City Creek Room

List of Talks:

- **Effect of stochasticity in a slow-fast predator-prey system**  
  Susmita Sadhu*, Christian Kuehn

- **Predicting Complex Ecosystem Dynamics without Measuring All Aspects**  
  Nicholas LaRacuente*, James O’Dwyer

- **How eco-evo feedbacks and species genetic variation drive eco-evolutionary predator-prey cycles**  
  Michael Cortez

- **Chemical mimicry or crypsis - evolutionary game played by parasitic ants**  
  Shinsuke Satoi*, Yoh Iwasa

- **Modeling evolution of post-menopausal human longevity: Grandmother Hypothesis**  
  Peter Kim*, John McQueen, Kristen Hawkes

- **A stochastic model for water-vegetation systems and the effect of decreasing precipitation on semi-arid environments**  
  Shannon Dixon, Nancy Huntly, Priscilla Greenwood, Luis F. Gordillo*

- **Modeling individual growth in Cross Timbers forest oaks**  
  Sean M. Laverty*, Chad B. King

- **Management of tropical forests in Indonesia: agroforestry and profit-sharing for combating illegal logging**  
  Yuki Kubo*, Joung-Hun Lee, Takahiro Fujiwara, Yoh Iwasa
A. Authors:

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B. Title: Effect of stochasticity in a slow-fast predator-prey system

Abstract

We study the effect of stochasticity, in the form of Gaussian white noise, in a three species predator-prey model with two distinct time-scales. The interactions between the three species is modeled by a system of slow-fast Itô stochastic differential equations. We explore the effect of noise near the onset of the singular Hopf bifurcation. The stochastic model admits several kinds of noise driven mixed-mode oscillations that capture the intermediate dynamics between two cycles of population outbreaks of the prey. We study the distribution of the random number of small oscillations between two large oscillations, which can be related to the return time between the outbreaks.
SMB 2017 Contributed Talk Abstract

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B. Title: Predicting Complex Ecosystem Dynamics without Measuring All Aspects

Abstract: Ecosystems typically involve more variables than would be practical to measure directly, including abiotic factors and unobserved taxa. We develop a theory that accounts for these hidden variables without including a needlessly large parameter space, despite not knowing the functional form of interactions in advance. We address these challenges using a new method that combines ideas from Empirical Dynamic Modeling with Sparse Identification of Non-linear Dynamics. We show how it is possible to make quantitative predictions about complex biological systems without prior knowledge of the functional form or extent of hidden factors. We consider how these “model-free” approaches can then inform the construction of more traditional mechanistic models. We examine real-world time series from the classic lynx-hare and paramecium-didinium predator-prey systems as well as more complicated ecosystems. We address limitations of previous equation-free techniques, including longer-term predictions and non-stationary processes.
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B. Title and Abstract
Title:
How eco-evo feedbacks and species genetic variation drive eco-evolutionary predator-prey cycles

Abstract:
Evolution in predators, prey, or both species can alter system stability and the characteristics of predator-prey cycles. For example, in the absence of evolution, predator oscillations lag behind prey oscillations by a quarter period. In contrast, evolution in one species can increase the lag to a half period and coevolution can cause predator peaks to occur before prey peaks. However, in an empirical rotifer-algae system (Becks et al. 2010, Ecology Letters) cyclic dynamics depended on the amount of prey genetic variation: the system was stable when prey genetic variation was low and exhibited cycles only when prey genetic variation was high. This leads one to ask, “When and through what mechanisms does increased genetic variation in one or more species alter system stability?”

This talk identifies how system stability depends on (i) the amount of genetic variation in predator and prey populations and (2) the ecological, evolutionary, and eco-evolutionary feedbacks in the system. I show how system stability can be decomposed into ecological, evolutionary, and eco-evolutionary feedbacks using the Routh-Hurwitz criteria. I then show how the strengths of the feedbacks depend on the amounts of prey and predator genetic variation, and how that information can be used to identify biological mechanism driving cycles in predator-prey system. This work unifies and explains empirical and theoretical studies on eco-evolutionary predator-prey systems and is a step towards understanding how eco-evolutionary feedbacks and variation within species alter community dynamics.
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B. Title: Chemical mimicry or crypsis – evolutionary game played by parasitic ants

B. Abstract: Some ant species are specialized in parasitism. They intrude nests of other ants and steal food, larvae, and eggs. They need to evade detection by patrolling hosts who attack detected invaders. Ants distinguish invaders from individuals of their own nest by the cuticular hydrocarbon profile. Individuals in the same nest have a similar mixture of coating chemicals. Some parasites adopt mimicry, and use a mixture of chemicals with the composition similar to their hosts. Other parasites adopt crypsis and have reduced amount of chemicals. In this paper, we develop a mathematical model to discuss the conditions in which these two strategies evolve. Assumptions are: both parasites and hosts are ants who have their own colonies. Host ants distinguish their nest-mates from parasites by the difference in chemical traits which are represented on multi-dimensional space. Parasitic ants engage in competition with other colonies of the same species, and competition is more intense between colonies of similar chemical traits, jeopardizing the advantage of cryptic parasites. We define parasites’ fitness and discuss evolution of their chemical strategy. Results are: cryptic parasites evolve under weak competition among colonies, and abundant host colonies. Mimic parasites evolve in the opposite conditions. Cryptic parasites and mimic parasites may coexist when recognition ability of host is limited.
A. Authors

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Kristen Hawkes
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B. Title and Abstract

Title
Modeling evolution of post-menopausal human longevity: Grandmother Hypothesis

Abstract

Post-menopausal longevity makes humans unique among primates, but how did it evolve? The Grandmother Hypothesis proposes that as grasslands spread in ancient Africa, it displaced foods that ancestral juveniles could exploit, but opened a new fitness opportunity when older females began subsidizing grandchildren. As more robust elders could help more descendants, selection favored increased longevity while maintaining the ancestral end of female fertility.

We develop a probabilistic agent-based model that incorporates two sexes and mating, fertility-longevity tradeoffs, and the possibility of grandmother help. Using this model, we show how the grandmother effect could have driven the evolution of human post-menopausal longevity. Simulations reveal two stable life-histories, one human-like and the other like our nearest cousins, the great apes. The probabilistic formulation shows how stochastic effects can slow down and prevent escape from the ancestral condition, and it allows us to investigate the effect of mutation rates on the trajectory of evolution.
SMB 2017 Contributed Talk Abstract

A. Authors

Presenter is in **bold**.

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B. **Title:** A stochastic model for water-vegetation systems and the effect of decreasing precipitation on semi-arid environments.

**Abstract:** Current climate change trends are affecting the magnitude and recurrence of extreme weather events. In particular, several semi-arid regions around the planet are confronting more intense and prolonged lack of precipitation, slowly transforming parts of these regions into deserts in some cases. We present a stochastic differential equations model for precipitation-vegetation interactions for semi-arid landscapes, derived from an individual based model. Extensive simulations suggest that observed trends of precipitation reduction in semi-arid landscapes might expedite desertification processes by several decades.
A. Sean M. Laverty (presenter),
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Chad B. King,
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B. (a) Title: Modeling individual growth in Cross Timbers forest oaks
(b) Abstract: Historically dominated by oak species, forest composition in the Oklahoma Cross Timbers ecoregion is changing, likely due to changes in fire management, climate, and land use. As part of a larger study aimed at cataloging diversity and establishment of seedlings and their recruitment into the forest understory and canopy, we present and analyze mathematical models of stem (trunk) growth of trees in the extant overstory. We fit these models to increment core data and describe trends in growth and in growth parameters with respect to age (of an individual) and time (across trees of all ages in a given year).
A. Authors
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B. Title and Abstract
Title
Management of tropical forests in Indonesia: agroforestry and profit-sharing for combatting illegal logging

Abstract
Illegal logging is a very serious problem for plantation management in tropics. Here we study the role of the profit sharing and agroforestry as management strategies in mathematical models. The owner chooses the age of trees to cut, and the local people choose their monitoring effort to prevent illegal logging. After the trees were removed, either by cutting, physical disturbances, or illegal logging, the owner hires local people to replant young trees. While trees are young, the land is also used as agriculture. In addition, the owner may share a fraction of profit obtained by selling logs with the workers. Illegal logging may be prevented by hiring forest guards or by monitoring effort of the workers. Results are: (1) If the discount rate is high, the foresters may use the land for continual agriculture by cutting trees at their young ages. (2) Under the presence of illegal logging pressure, the owner may find it profitable to share the income with the workers to solicit their monitoring efforts. (3) An increased cost of replanting makes local people reluctant in participating in surveillance activity, and makes owner increase the profit-sharing rate to encourage their participation. We discuss policy implications of these results.
CS6: Immunology

Tuesday, July 18
10:30–12:30
Alpine Room

List of Talks:

- *Density-Dependent Viral Clearance During Respiratory Virus Infections*
  Veronika Bernhauerova*, Margaret Myers, Amanda P. Smith, Robert Torrence, Matthias Chung, Robert Michael, David J. Moquin, Stacie Woolard, Charles Russell, and Amber M. Smith

- *Modeling original antigenic sin in dengue viral infection*
  Ryan Nikin-Beers*, Stanca Ciupe

- *Modeling HIV infection in the Brain*
  Naveen K. Vaidya

- *Application of Mathematical Model of the Inflammatory Response in Pathogen Infections*
  Wenjing Zhang*, Linda J. S. Allen, Sophia Jang

- *Mathematical modeling of immune self tolerance in the Thymus: deletion vs Treg differentiation*
  James Moore*, Rustom Antia

- *A model of cancer induced T cell exhaustion*
  Heidi Dritschel*, Helen Byrne, Sarah Waters, Andreas Roller

- *A model of tumor-immune interactions including T cells, NK cells and MDSCs*
  Victoria Gershuny*, Ardith El-Kareh, Tim Secomb

- *Synergy through nonlinearity: a model for supereffect T cell generation by immunotherapy*
  Anna Konstorum*, Anthony T. Volča, Adam J. Adler, Reinhard C. Laubenbacher
Density-Dependent Viral Clearance During Respiratory Virus Infections

Veronika Bernhauerova\(^1\), Margaret Myers\(^1,2\), Amanda P. Smith\(^1\), Robert Torrence\(^3\), Matthias Chung\(^3\), Robert Michael\(^1\), David J. Moquin\(^1\), Stacie Woolard\(^1\), Charles Russell\(^1\), and Amber M. Smith\(^1\)

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Respiratory infections caused by influenza A virus (IAV) or parainfluenza virus (PIV) cause a significant amount of morbidity and mortality each year. Understanding how virus is controlled by immune responses is critical to combatting these infections and developing effective therapeutics. To understand the mechanisms of viral control, we infected mice with either influenza A/PR8 or mouse adapted PIV (sendai virus) and measured viral loads and CD8 T cells over the infection course. We then developed two kinetic models that quantify the different phases of viral decay, and used a rigorous ensemble method to fit the models to our data. Our models implicitly or explicitly account for CD8 T cell-mediated viral clearance and indicate that IAV and PIV are cleared in a density-dependent manner regardless of mechanism. Each model exhibits strong sensitivity to changes in select parameters involved in infected cell clearance, which significantly affect infection duration and viral loads. We further examined parameter behavior to determine how the models are related and better interpret the results of models that implicitly account for viral control in cases where immunological data is absent. Together, our models provide well-characterized representations of respiratory infection dynamics and insight into the regulation of IAV and PIV control.
A. Authors

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B. Title and Abstract

Modeling original antigenic sin in dengue viral infection

Cross-reactive T cell responses induced by a primary dengue virus infection may contribute to increased disease severity following heterologous infections with a different virus serotype in a phenomenon known as the original antigenic sin. In this study, we developed and analyzed in-host models of T cell responses to primary and secondary dengue virus infections that considered the effect of T cell cross-reactivity in disease enhancement. We fit the models to published patient data and showed that the overall infected cell killing is similar in dengue heterologous infections, resulting in dengue fever and dengue hemorrhagic fever. The contribution to overall killing, however, is dominated by non-specific T cell responses during the majority of secondary dengue hemorrhagic fever cases. By contrast, more than half of secondary dengue fever cases have predominant strain-specific T cell responses with high avidity. These results support the hypothesis that cross-reactive T cell responses occur mainly during severe disease cases of heterologous dengue virus infections. We further describe how we may incorporate these results into an immuno-epidemiological model of dengue viral infection.
Contributed Talk

A. Author: Naveen K. Vaidya, University of Missouri – Kansas City, Missouri, USA (Email: nvaidya.anyol@gmail.com) [Presenter]

B. Title And Abstract:

Title: Modeling HIV infection in the Brain

Abstract: Human Immunodeficiency Virus (HIV) infection in the brain causing several neurological disorders is one of the least understood mechanisms of HIV biology. In this talk, I will present a novel mathematical model that can describe virus dynamics seen in the experimental data from the brain of macaques infected with Simian Immunodeficiency Virus (animal model of HIV). Using our model, we identify key parameters related to the brain infection, including virus-transfer across blood-brain barrier. Furthermore, we compute the basic reproduction number that provides a threshold for the establishment of infection, and compare the viral infection dynamics in the brain with that in the plasma.
Application of Mathematical Model of the Inflammatory Response in Pathogen Infections

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Abstract

Inflammatory response in pathogen infections has distinct differences in humans and their natural reservoirs for Avian Influenza, Dengue, Hantavirus, and SARS-CoV. Taking Hantaviruses for example, the infection persists in natural rodent reservoirs and may last the life of the animal. While the spillover infection to humans results in severe, life threatening disease, such as acute lung injury, respiratory failure, sepsis, and a cytokine storm. Simple ODE and SDE models with pro-inflammatory and anti-inflammatory cytokines are studied to investigate underlying causes and reveal potential mechanisms. The bifurcation analysis on ODE model demonstrates an array of dynamical behaviors of the inflammatory response in pathogen infections. With the increase of the control efforts from anti-inflammatory cytokines, (1) pro-inflammatory cytokines first stabilizes in high level concentration, (2) they have the possibility to drop to a low level concentration showing bistability, (3) then they oscillate between low and high level concentrations, (4) further they spend a longer time in the low concentration with periodic flare-ups. Further random changes are considered in two corresponding stochastic differential equations (SDE) models. The SDE simulations show flare-ups in pro-inflammatory cytokines concentration with the same input of parameter values and initial conditions generating bistable behavior in the deterministic ODE model. Furthermore, the uniform period and amplitude of recurrent cycles produced from the ODE model become time-varying in the simulation of SDE model. The analysis results demonstrate the distinct inflammatory responses in pathogen infections in human and non-human species due to interactions between pro- and anti-inflammatory cytokines. These findings are consistent with the fact that people with healthy immune systems are more likely to produce high levels of pro-inflammatory cytokines in infection, thereby initiate cytokine storm. The results also give an potential explanation to no significant symptom in Hantavirus natural rodent reservoirs.
Mathematical modeling of immune self tolerance in the Thymus: deletion vs Treg differentiation

Self reactive T cells, which respond to antigens originating from our own tissues, have the potential to cause autoimmune disease unless they are deleted or inactivated. In the Thymus, newly formed T cells interact with dendritic cells (DCs) presenting self antigens as a first line of defense against autoimmune disease. A T cell that reacts with a self antigens may either die or become a regulatory T cell (Treg) depending on factors which are not yet understood. We model various proposed mechanisms of T-cell deletion and Treg differentiation. We propose that multiple contacts between T-cells and DCs are required to efficiently maintain tolerance to self antigens.
SMB 2017 Contributed Talk Abstract

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B. Title and Abstract:
A model of cancer induced T cell exhaustion

During an immune response against an acute infection, checkpoint-inhibitory receptors (e.g. Programmed Death 1 and Cytotoxic T Lymphocyte Antigen-4 receptors) are transiently up-regulated by T cells to moderate the magnitude of the response to protect the tissue from damage. These receptors also protect against auto-immunity (attack of healthy cells). In chronic infections such as cancer, T cells become exhausted due to continuous exposure to high levels of tumour antigen. Such exhausted T cells are distinguished from their normal counterparts by sustained expression of checkpoint inhibitory receptors.

The appropriate choice of treatment for a given degree of exhaustion is a major question faced by cancer researchers today. In recent years, the potential of harnessing the immune system to combat cancer and has shown remarkable results even for aggressive cancers such as metastatic melanoma. However not all patients respond. A greater understanding of the underlying dynamics for patients with varying degrees of T cell exhaustion is necessary.

In this work we propose a mathematical model on how varying degrees of T cell exhaustion affect the long-time behaviour of tumour-immune cell interactions. Here we assume that the system is well mixed and propose a system of ordinary differential equations to describe four cell populations: exhausted T cells, functional T cells and T cell resistant and non-resistant tumour cells. Our mathematical model provides the time evolution of the relevant cell populations and permits a qualitative examination of the effect of T cell exhaustion on patients with immunocompromised, normal and high functioning immune systems. One key finding of this work is that the possible patient outcomes depend crucially on the level of exhaustion. Namely, for a normal functioning immune response, patients with moderate levels of exhaustion may exhibit the most diverse range of outcomes, with tumour elimination, control and escape all possible. By contrast, patients with low levels of exhaustion do not exhibit a control state, and patients with high levels of exhaustion only exhibit control or escape states.

C. Area: Dynamical systems, immunology

D. Additional information: Yes I would be willing to submit a poster if there isn't sufficient room in the schedule for a talk.
A model of tumor-immune interactions including T cells, NK cells and MDSCs

In recent years, advances in cancer research have shown that the body’s immune response to tumor cells plays a significant role in fighting cancer growth. Although the immune system is intrinsically capable of destroying tumor cells, tumors and their microenvironment have an ability to suppress the immune response. Tumors promote direct immunosuppression through various mechanisms, such as recruitment and stimulation of regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Tumors also evade the immune response through several mechanisms, such as modulation of antigen expression. Chemotherapy has been shown to combat some of those mechanisms through various immunogenic effects, including release of antigens by dying tumor cells or reductions in immunosuppressive subpopulations such as Tregs and MDSCs, in addition to direct cytotoxicity. For example, the drug combination FOLFOX (5-fluorouracil, oxaliplatin and leucovorin) which is in wide clinical use for colorectal carcinoma, affects both natural killer (NK) cells—via oxaliplatin—and MDSCs—via 5-fluorouracil.

In order to understand the complex interplay between therapy, the tumor, and the immune system, it is necessary to develop a model of tumor growth that includes these immune subpopulations and their interactions with the tumor and with each other. Here, such a model is presented, consisting of 17 coupled ordinary differential equations, accounting for the tumor as well as CD4+ and CD8+ T cells, Tregs, NK cells, dendritic cells, MDSCs, and both immunostimulatory (IL-2, IFN-gamma) and immunosuppressive (IL-10, TGF-beta) cytokines or factors. Crosstalk, such as that between NK cells and dendritic cells, and between MDSCs and T cells, is included, and other new effects include the recruitment of Tregs to the tumor site by MDSCs and maturation of MDSCs into dendritic cells. All parameters are estimated from experimental data. Predicted cell counts and plasma levels over time are compared to experimentally measured values in human patients. The model is consistent with experimental studies that show that, in the absence of treatment, NK cells have less direct cytotoxic effect in the tumor than CD8+ effector T-cells, but that an order-of-magnitude increase in NK cell recruitment could increase NK-induced cytotoxicity significantly, suggesting opportunities for immunotherapy. Implications for considering immunologic effects of standard chemotherapy combinations, in particular FOLFOX for colorectal cancer, are discussed, as are extensions of the model to a metastatic tumor.
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B. Title and Abstract

Synergy through nonlinearity: a model for supereffector T cell generation by immunotherapy

Combined agonist stimulation of the CD8+ T cell costimulatory receptors OX40 (CD137) and 4-1BB (CD134) has been shown to generate ‘supereffector’ T cells that survive longer and produce a greater quantity of cytokines that mediate tumor cell killing in vivo compared to T cells stimulated with an agonist of either costimulatory receptor individually. In order to understand the mechanisms for this synergy, we have created a mathematical model for the activation of the CD8+ T cell intracellular signaling network by mono- or dual-costimulation (DCo) and show that synergy by DCo results from nonlinear interactions between intermediate signaling components. In silico simulation of the model with and without knock-out experiments supports published experimental results. We propose that, in a more general setting, these types of nonlinear interactions can play a key role, and thus be exploited, for maximizing synergy in designing combination immunotherapies.
CS7: Physiology

Tuesday, July 18
10:30–12:30
Commander’s House South Parlor

List of Talks:

- *Disentangling active from passive diffusion in observations of motor-mediated transport*
  Christopher E. Miles*, Olaolu Osunbayo, James P. Keener, Michael Vershinin

- *A Theory that Predicts Behaviors of Disordered Cytoskeletal Networks*
  Julio M Belmonte*, Maria Leptin, Francois Nedelec

- *Turing mechanism for homeostatic control of synapse density during C. elegans growth*
  Heather Brooks*, Paul Bressloff

- *Hybrid cellular Potts model including focal adhesions as catch bond clusters explains cell response to substrate stiffness*
  Elisabeth G. Rens*, Roeland M.H. Merks

- *Elasticity and diffusion in nuclear pore transport*
  Ben Fogelson*, James Keener

- *Mathematical model of glucose metabolism and lactate production in the kidney*
  Ying Chen*, Brendan C. Fry, Anita Layton

- *Trust your gut: Maintenance of the pH gradient in the gastric mucus layer*
  Owen L. Lewis*, James P. Keener, Aaron L. Fogelson
Disentangling active from passive diffusion in observations of motor-mediated transport

Christopher E. Miles*
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Intracellular transport is involved in a wide array of investigations at the cellular level. In such cases, it is essential to understand the underlying cause of cargo mobility. This is typically assessed by tracking a particle and characterizing the statistics of motion, often through a mean-squared displacement (MSD) analysis. One convenient feature of this technique is that active (ballistic) transport is easily distinguished from diffusive, as the resulting MSD curves are quadratic and linear respectively. In this work, we show that mechanochemical enzymes (such as motors) can drive motion in a statistically diffusive manner (active diffusion), which could be easily overlooked and lumped together with passive diffusion. From the theory, we provide (i) statistical markers that can be used as clues that motion may be from active rather than passive diffusion (ii) an experimental setup to definitively distinguish between the two.
A. AUTHORS

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B. TITLE AND ABSTRACT

A Theory that Predicts Behaviors of Disordered Cytoskeletal Networks

Morphogenesis in animal tissues is largely driven by tensions of actomyosin networks, generated by an active contractile process that can be reconstituted in vitro. Although cytoskeletal components and their properties are known, the requirements for contractility are still poorly understood and the problem of expansion driven by molecular motors has been neglected. Many mechanisms for contraction have been proposed, but they are limited in scope and not predictive. Here, we describe a theory that is able to predict whether an isotropic network will contract, expand, or conserve its dimensions, depending on the activities of the elements that connect the filaments. This analytical theory correctly predicts the behavior of percolated networks, and reveals conditions under which networks of rigid filaments are either contractile or expansile. It also predicts contractility as a function of parameters such as network density or binding rates and explains why contractility requires both crosslinkers and motors. Our results suggest that pulsatility is an intrinsic behavior of contractile networks if the filaments are not stable but turn over. The theory offers an unifying framework to think about mechanisms of contractions or expansion. It provides a foundation for the study of a broad range of processes involving cytoskeletal networks, and a basis for designing synthetic networks.
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2. Title and Abstract
Turing mechanism for homeostatic control of synapse density during C. elegans growth

We propose a novel mechanism for Turing pattern formation that provides a possible explanation for the regular spacing of synaptic puncta along the ventral cord of C. elegans during development. The model consists of two interacting chemical species, where one is passively diffusing and the other is actively trafficked by molecular motors. We identify the former as the kinase CaMKII and the latter as the glutamate receptor GLR-1. We focus on a one-dimensional model in which the motor-driven chemical switches between forward and backward moving states with identical speeds. We use linear stability analysis to derive conditions on the associated nonlinear interaction functions for which a Turing instability can occur. We find that the dimensionless quantity $\gamma = \frac{\alpha d}{v^2}$ has to be sufficiently small for patterns to emerge, where $\alpha$ is the switching rate between motor states, $v$ is the motor speed, and $d$ is the passive diffusion coefficient. One consequence is that patterns emerge outside the parameter regime of fast switching where the model effectively reduces to a two component reaction-diffusion system. Furthermore, we show that these patterns are maintained during domain growth, which points to a possible mechanism for synapse density maintenance in C. elegans.
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Title
Hybrid cellular Potts model including focal adhesions as catch bond clusters explains cell response to substrate stiffness

Abstract
Pattern formation and individual cell behavior in tissues depends on mechanical extracellular matrix (ECM) parameters, including stiffness. Cellular response to ECM stiffness include changes in cell shape: on soft substrates, cells are generally small and rounded, while on stiffer substrates cells assume spindle-like shapes, and on glass-like substrates cells generally spread out like pancakes. This behavior has been observed for many cell types, including fibroblasts and endothelial cells. Here we introduce a mathematical model to explain how substrate stiffness regulates cell shape. Stiffness sensing is mediated through transmembrane integrin molecules, which behave as ‘catch bonds’ whose strength increases under tension. Focal adhesions, large assemblies of integrins, grow larger on stiffer substrates. We extended a current hybrid cell-based continuum model (van Oers, Rens et al. PCB 2014, Rens and Merks BJ 2016) to describe such molecular mechanics. The model includes 1) A finite-element model for the ECM; 2) a cellular Potts model, to describe cell shape changes; 3) a set of ordinary-differential equations describing the growth and decay of individual focal adhesions, based on a published model (Novikova and Storm, BJ 2013). In this model, cells move and pull on the ECM. This leads to a slow build-up of tension on the FA, which changes the FA's size. The focal adhesions finally inhibit the cell's pseudopod retractions from the ECM. These minimal model assumptions reproduce the observed cell shape behavior on substrates of varying stiffness. On soft substrates, tension builds up slowly, such that the focal adhesions cannot grow and the cell cannot spread. On stiffer substrates, a symmetry breaking occurs in which random protrusions can generate enough tension so that focal adhesions will grow. This further promotes tension generation and cell spreading in this direction, thus driving cell elongation. On rigid substrates, focal adhesions will grow everywhere around the cell membrane, so that cells start to spread. Our model result increases our understanding of the molecular mechanism behind cell shape changes in response to ECM stiffness. Our model can be further extended to study the effect of cyclic stretching on cell orientation or to study tissue patterning in response to ECM stiffness or different type of integrins.
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B. Title and Abstract
Title: Elasticity and diffusion in nuclear pore transport
Abstract: The nuclear pore complex controls transport between the nucleus and the cytoplasm. Much of this transport is driven by thermal fluctuations, not by an active input of energy, and yet the nuclear pore complex achieves high throughput of cargo while efficiently filtering out macromolecules that should not be transported. Physical motion of objects through the pore is controlled by a collection of disordered, flexible polymers filling the pore channel. We present a mechanical model for motion through this collection of polymers, with results for the effective speed of various cargos.
MATHEMATICAL MODEL OF GLUCOSE METABOLISM AND LACTATE PRODUCTION IN THE KIDNEY

YING CHEN (PRESENTER)♮ BRENDAN C. FRY† ANITA LAYTON‡

Abstract. The metabolism of glucose provides most of the ATP required for energy-dependent transport processes. In the inner medulla of the mammalian kidney, limited blood flow and O₂ supply yield low oxygen tension; therefore, a substantial fraction of the glucose metabolism in that region is anaerobic. Lactate is considered to be a waste product of anaerobic glycolysis, which yields two lactate molecules for each glucose molecule consumed, thereby likely leading to the production and accumulation of a significant amount of lactate in the inner medulla. To gain insights into the transport and metabolic processes in the kidney, we have developed a detailed mathematical model of the renal medulla of the rat kidney. The model represents the radial organization of the renal tubules and vessels, which centers around the vascular bundles in the outer medulla and around clusters of collecting ducts in the inner medulla. Model simulations yield significant radial gradients in interstitial fluid oxygen tension and glucose and lactate concentrations in the outer medulla and upper inner medulla. In the deep inner medulla, interstitial fluid concentrations become much more homogeneous, as the radial organization of tubules and vessels is not distinguishable. Using this model, we have identified parameters concerning glucose transport and basal metabolism, as well as lactate production via anaerobic glycolysis, that yield predicted blood glucose and lactate concentrations consistent with experimental measurements in the papillary tip. In addition, simulations indicate that the radial organization of the rat kidney may affect lactate buildup in the inner medulla.

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- Aaron L. Fogelson, University of Utah, 155 S. 1400 E. Room 233, Salt Lake City, UT 84112-0090. fogelson@math.utah.edu

B Title and Abstract

Trust your gut: Maintenance of the pH gradient in the gastric mucus layer

The gastric mucus layer is widely recognized to serve a protective function, shielding your stomach wall from the extremely low pH and digestive enzymes present in the stomach lumen. Often described as a "diffusion barrier," the mucus is believed to hinder the transport of small diffusive species from the stomach interior (lumen), to the wall (mucosa). However, there is no consensus on the mechanism by which the mucus layer hinders lumen-to-wall transport while allowing acid and enzymes secreted from the mucosa unimpeded transport to the lumen. Using physical principles, we develop a mathematical description of electro-diffusion within a two-phase gel, and use it to test physiological hypotheses that are beyond current experimental techniques. Furthermore, we explore what regulatory mechanisms are necessary to segregate an acidic stomach interior from a neutral stomach wall.
CS8: Data Science
Tuesday, July 18
10:30–12:30
Bonneville Room

List of Talks:

- **Using correlated provinces to predict dengue incidence in Thailand**
  Lindsay T. Keegan*, Nicholas Reich, Derek A.T. Cummings, Sopon Iamsirithaworn, Joshua Kaminsky, Soawapak Hinjoy, Justin Lessler

- **A Markov Model for Antibiotic Use and Decision Making**
  Karim Khader*, Makoto Jones, Christopher Graber, Peter Glassman, Matthew Goetz

- **Challenges in modeling temporal dynamics of microbiomes**
  Christopher H. Remien*

- **The impact of temporal resolution on parameter inference for biological transport models**
  Jonathan Harrison*, Ruth Baker

- **Robust cell tracking in epithelial tissues through identification of maximum common subgraphs**

- **Uncovering functional relationships in leukemia**
  Gregory K. Behbehani, Kevin R. Coombes, Reginald L. McGee*

- **How Shapes of Nucleosomal DNA Regulates Gene Expression**
  Sergiusz Wesolowski*, Jorge Martinez, Wei Wu, Daniel Vera
1 A. Authors

Lindsay T. Keegan, Nicholas Reich, Derek A.T. Cummings, Sopon Iamsirithaworn, Joshua Kaminsky, Soawapak Hinjoy, Justin Lessler

2 B. Title and Abstract

Using correlated provinces to predict dengue incidence in Thailand

Accurate infectious disease forecasting systems have the potential to improve the public health response to epidemics and epidemic diseases. Dengue is an important public health problem causing an estimated 390 million infections each year. Dengue is endemic in Thailand, characterized by cyclic epidemic activity. Although a vaccine has recently been made available for dengue, dengue control in Thailand is limited to case management and vector control. Thus, the ability to reliably forecast dengue incidence could play an integral part of improving the public health response.

Using 43 years of DHF incidence data in Thailand, we explore forecasting future incidence in each of the 77 provinces using current and past incidence in other provinces. We use a modified Poisson auto-regressive model with lag time and the number of correlated provinces as parameters. We systematically cross validate the performance of using correlated provinces at different time lags to predict DHF incidence for two model frameworks, using absolute case counts and using changes in the number of cases. We evaluate the performance of our models using the mean absolute scaled error, comparing our models to both the seasonal median and to predicting the previous observation.

We test our method for three scenarios: we predict a single randomly missing observation, we forecast a run of missing data during an epidemic, and we forecast ahead a year of missing data. We show that our method of using leading and contemporaneous observations is a successful approach for both imputing missing data and forecasting incidence. We find that across all three experiments, including up to ten correlated provinces at a time lag of 1-3 bi-weeks consistently performed the best and out performed both baseline models. We present a single integrated framework that can be used to impute missing data and forecast disease incidence and show that our method has strong performance relative to either of the two baseline models. We demonstrate the utility of geographic data as a valuable source of information for disease forecasting systems. Although we demonstrate the efficacy of this method for DHF in Thailand and identify specific parameters to optimize the model fit, we believe it to be flexible enough to be applied in a variety of different contexts to both dengue and other diseases.
SMB2017 Abstract Submission

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Title: A Markov Model for Antibiotic Use and Decision Making

Abstract

Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections according to the Centers for Disease Control and Prevention, and have a significant impact on healthcare systems. Antibiotics have been used for 70 years and have greatly reduced illness and death from these infectious diseases, however antibiotic exposure is known to select for antibiotic resistant organisms and recent studies have demonstrated that there exists a wide variation in antibiotic use. The decision to do of when use antibiotics should account for their impact both at the individual-level and population-level. However knowledge about appropriate use of antibiotics is limited, and there is no framework to match potential excess in antibiotic use with rational intervention approaches.

We used a framework of three decision points for better understanding and intervening on antibiotic use. Choice corresponds to the initial choice of antibiotic, Change represents the decision to de-escalate, escalate, or stop antibiotics generally around antibiotic day 3, and Completion is the decision of how long to give antibiotics. To map to the Choice, Change, and Completion framework, choice was estimated by the probability of starting antibiotics on hospital day 1 or day 2. Change was estimated by the probability of stopping antibiotics averaged across hospitalization. Completion was not represented because inpatient antimicrobial use metrics do not consider post-discharge prescriptions. These statistics were estimated by facility and by antibiotic group. We used a discrete-time Markov chain to model the Choice and Change framework in mathematical terms and demonstrate the relationship between each estimated parameter and overall measures of antibiotic use (AU), given as days of therapy per 1000 patient-days (DOT/1000 PDs). Time was given in hospital days and the probabilities of transitions were assumed to be constant, before and after the third hospital day. We treated hospital discharge as an absorbing state, therefore making use of the general theory for Absorbing Markov chains to obtain a model estimate for AU (= 1000 × E[Time on antibiotics]/E[Time before discharge]).

Data were included from patients admitted to one of 131 acute care facilities during calendar year 2012. Facility-level antimicrobial use was classified as one of: 1. Anti-MRSA; 2. Broad-community; 3. , Broad-hospital; and 4. Surgical site infection prophylaxis (SSIP). The Pearson correlation coefficients between the observed AU and predicted AU based on the Markov chain were 0.95 for Anti-MRSA, 0.95 for Broad Hospital, 0.89 for Broad Community, and 0.88 for SSIP. Overall, the probability of going on antibiotics is 5% within the first two days and 3% thereafter. The probability of stopping antibiotics on any given day is 24%, and the overall estimate of AU is 118 DOT/1000 PDs. Our model suggests that a reduction in the probability of starting antibiotics after day 3 by 1% would reduce AU by 18 DOT/1000 PDs while an increase in the probability of stopping antibiotics by 1% would only reduce AU by 3 DOT/1000 PDs.

Despite some simplifying assumptions, this model of antibiotic use correlates well with observed antibiotic use. We have also presented it in a way that relates to decision points and provides a way that may help tailor policy at different facilities. For instance, a user could quickly solve optimization problems to help identify optimal strategies for reducing antibiotic use when necessary. To our knowledge, antibiotic use has not yet been described and presented in this way. This model and its ability to influence good stewardship practices will need to be further investigated in studies.
**Authors:** Christopher H. Remien

**Title:** Challenges in modeling temporal dynamics of microbiomes

**Abstract:** Microbes are found in nearly every environment on Earth, performing vital tasks for the health of ecosystems, organisms, and the environment. Low-cost, high-throughput sequencing technologies now allow for the rapid and relatively cheap assessment of the composition of microbial communities over time. Despite tremendous advances in our understanding of the composition of microbiomes, there is still much to learn regarding biological function and how microbiomes can be manipulated to provide ecosystem services to their host or environment. There is growing interest in moving beyond simply characterizing microbial diversity to understanding the factors that shape functional and dysfunctional microbiomes. The challenge of understanding growth trajectories in microbial communities are manifold. Data are noisy, based on observation rates within a sequencing run, relatively limited in terms of sampling points, and very large in terms of number of species (100s to 1000s). To overcome some of these issues, we have developed a method that uses an ARIMA model with Poisson errors fit with elastic-net regularization to estimate robust and predictive models models of microbiome dynamics. We compare this approach to similar methods based on generalized Lotka-Volterra equations.
Title: The impact of temporal resolution on parameter inference for biological transport models.

Abstract: When collecting time series data of biological transport processes, it is generally necessary to observe the system at discrete time points, for example via an imaging experiment. This can introduce errors when the motion of an observed object is approximated with discrete steps. We study the impact of collecting data at different temporal resolutions on parameter inference for biological transport models. In this work, we have performed exact inference for velocity jump process models in a Bayesian framework. This allows us to obtain estimates of the model parameters, including the turning rate and noise amplitude, based on noisy observations of this transport process. We show sensitivity of these estimates to changes in time discretisation and noise amplitude. For a fixed photon budget, our results suggest that better estimates of parameters can be obtained when imaging more frequently with more noise than imaging sparsely with low noise.
SMB 2017 Contributed Talk Abstract:

Robust cell tracking in epithelial tissues through identification of maximum common subgraphs

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Primary area: Data Analysis and Statistics  
Secondary area: Developmental Biology

Abstract:
Tracking of cells in live-imaging microscopy videos of epithelial sheets is a powerful tool for investigating fundamental processes in embryonic development. Characterising cell growth, proliferation, intercalation and death in epithelia helps us to understand how morphogenetic processes such as tissue invagination and extension are locally regulated and controlled. Accurate cell tracking requires correctly resolving cells entering or leaving the field of view between frames, cell neighbour exchanges, cell removals and cell divisions. However, current tracking methods for epithelial sheets are not robust to large morphogenetic deformations and require significant manual interventions. Here, we present a novel algorithm for epithelial cell tracking, exploiting the graph-theoretic concept of a ‘maximum common subgraph’ to track cells between frames of a video. Our algorithm does not require the adjustment of tissue-specific parameters, and scales in sub-quadratic time with tissue size. It does not rely on precise positional information, permitting large cell movements between frames and enabling tracking in datasets acquired at low temporal resolution due to experimental constraints such as phototoxicity. To demonstrate the method, we perform tracking on the \textit{Drosophila} embryonic epidermis and compare cell-cell rearrangements to previous studies in other tissues. Our implementation is open source and generally applicable to epithelial tissues.
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B. Title And Abstract:

Title: *Uncovering functional relationships in leukemia*

Abstract: Mass cytometers can record tens of features for millions of cells in a sample, and in particular, for leukemic cells. Many methods consider how to cluster or identify populations of phenotypically similar cells within cytometry data, but there has yet to be a connection between cell activity and other features and these groups or clusters. We use differential geometric ideas to consider how cell cycle and signaling features vary as a function of the cell populations. This consideration leads to a better understanding of the nonlinear relationships that exist in the cytometry data.
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[B] Title and Abstract:

**Title:** How Shapes of Nucleosomal DNA Regulates Gene Expression.

**Abstract:**

Nucleosomes positioning, histone modifications, and general nucleosome make-up are the underlying factors in affecting gene transcription, thus, understanding how nucleosomes are distributed can advance the field of genomics; ultimately, understanding how genes are expressed can equate to understanding the actual proteins that code for them. Despite of recent advances in technology of sequencing and experimental design, the full comprehension to which nucleosomes are arranged in DNA remains elusive. Untapping the full potential of the second and third generation sequencing experiments, and drawing sound inferences from such experiments, relies on appropriate mathematical methods that can capture the complexity of the structure of the underlying biological processes.

In this talk we describe a new elastic shape analysis framework based on Square Root Slope Functions to analyze Illumina sequencing experiments. The new model redefines experimental results as elastic shapes over reference genome. The shape interpretation allows us to establish the connection between changes of DNA arrangement around the nucleosome and the changes in the neighboring gene’s expression. The model explains how nucleosome shape and position can regulate gene activity.
CS9: Cancer Treatment
Wednesday, July 19
10:30–12:30
City Creek Room

List of Talks:

- A Novel Single-cell Variability Model for Heterogeneity in Cancer with Applications
  Arran Hodgkinson*, Ovidiu Radulescu

- Multi-Objective Design Optimization of Drug Nanocarriers Targeting Tumors
  Ibrahim M. Chamseddine*, Michael Kokkolaras

- Biomathematical proneural glioma model suggests giving PDGF inhibitors earlier
  Susan Christine Massey*, Peter Canoll, Kristin R. Swanson

- Predicting human pancreatic cancer cell growth with multiple doses of Schwarz measles virus
  Daniel N. Santiago*, Daniel Abate-Daga, Heiko Enderling

- Temporal Dynamics of Macrophages Plasticity in the Bone Microenvironment
  Etienne Baratchart*, Chen Hao Lo, Conor Lynch, David Basanta

- A model of natural selection predicts treatment resistance in prostate cancer
  John D. Nagy*

- Optimal chemotherapy scheduling based on a pair of collaterally sensitive drugs
  Nara Yoon*, Robert Vander Velde, Andriy Marusyk, Jacob G. Scott
A Novel Single-cell Variability Model for Heterogeneity in Cancer with Applications

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Abstract: Heterogeneity in cancer has been studied by both the mathematical and medical communities but with the vast majority of efforts concentrated on stepwise, discrete descriptions of oncogenesis. Herein, we employ a spatio-structural approach through which one can describe continuous variation within a population of cells. Endowing these cells with the ability to change their metabolic, or genetic, state in response to various environmental factors, one can permit the gradual transition of populations between states on a continuous structural spectrum, in line with recent biological descriptions.

Using the Liouville equation, we derive a novel class of models for the exploration of phenotypic switching in heterogeneous cancer populations, as well as the profiles of genetic or metabolic variation in structure space. We further present solutions on the structured population dynamics, based on the criteria of gradualistic versus punctuated evolutionary assumptions for the cell population. These assumptions give rise to a genetically and spatially heterogeneous population of cells, and make predictions with punctuated assumptions giving a closer comparison to the clinical and biological literature. Finally, we apply this model to the problem of genetic variation in heterogeneous tumours to produce a qualitative illustration of natural evasiveness to targeted drug strategies within heterogeneous cancer populations and present a novel drug strategy for further biological study.
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B Title and Abstract:

Multi-Objective Design Optimization of Drug Nanocarriers Targeting Tumors

Nanotherapy is an emerging cancer treatment which aims at reducing the systemic toxicity of conventional chemotherapy. It is based on delivering nanoparticles encapsulating anti-neoplastic agents to tumors in a targeted manner. The delivery efficiency, corresponding to the fraction of the injected nanoparticles that adhere to the tumor site, depends on nanoparticle size \(a\) and aspect ratio \(AR\), which are determining factors in the nanoparticle transport mechanisms from blood to tissue. Currently, these variables are chosen empirically, and may not yield optimal targeted drug delivery. In this respect, an optimization approach is desirable to obtain the optimal values of \(a\) and \(AR\). In this study, a computational model predicting the accumulation of blood-borne nanoparticles at tumor vessels is used to compute objective functions representing nanotherapy toxicity and efficacy. It considers a 2D \textit{in silico} tumor where blood flow is modeled as creeping flow and solved with consideration of non-Newtonian effects. It estimates the accumulation of nanoparticles using a nanoparticle-to-endothelium interaction model that takes into account the nanoparticle size, aspect ratio, ligand and receptors densities, binding affinities, and Brownian motion. It also quantifies the drug penetration into the tissue using diffusion-reaction equation. A preliminary full factorial design of experiments with respect to \(a\) and \(AR\) reveals that delivery efficiency increases as \(a\) and \(AR\) increase. However, maximizing delivery efficiency results in non-uniform drug distribution in the tumor, which impairs tumor recession. Therefore, a multi-objective optimization problem (MOO) is formulated to quantify the trade-off between nanoparticles accumulation and distribution. Gradients can be very challenging to approximate using simulation models. Therefore, the MOO is solved using the derivative-free Mesh Adaptive Direct Search algorithm. The obtained Pareto front consists of an infinite number of mathematically equivalent solutions to the MOO problem. However, interesting design solutions can be identified, e.g., an ellipsoid with major axis and aspect ratio of 720 nm and 7.45 respectively, as the solution closest to the utopia point (defined as the design point that would optimizes both objectives if they were not competing). A parametric study of the tumor vessels’ average wall shear stress shows that these optimizers are insensitive to moderate changes in the tumor microenvironment. This results in a design with potential to render nanoparticle structure a set parameter in future nanotherapeutic studies, thus helping experimentalists reduce their set of variables.
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B. Title and Abstract:
Title: Biomathematical proneural glioma model suggests giving PDGF inhibitors earlier

Abstract: Platelet derived growth factor (PDGF) is often over-expressed in gliomas, where it can drive tumor growth via autocrine and paracrine stimulation of PDGF receptor (PDGFR)–expressing glioma cells, as well as paracrine recruitment of non–neoplastic oligodendroglial progenitor cells (OPCs), which also express PDGFRs. To date, the use of PDGF inhibitors has remained largely unsuccessful at improving patient outcomes in glioblastoma; however, this may be due to inadequate targeting of these agents to the best candidates. Using a mathematical model of PDGF–driven glioma growth, we explore which patients might receive the greatest benefit from PDGF–targeted therapies. By incorporating different treatment simulations in our model, we show that PDGF inhibition results in decreased OPC recruitment, which leads to slower growing, but more diffusely infiltrating tumors. This suggests that PDGF inhibitors may be most effective at treating patients with more rapidly proliferating tumors that show a predominance of OPCs on immunohistochemistry. Further, the model suggests that they should be given earlier in the disease course, i.e., prior to recurrence, but following resection.
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B. Title and Abstract

Predicting human pancreatic cancer cell growth with multiple doses of Schwarz measles virus

Human pancreatic cancer has a 5-year survival of 7%. An appealing therapy is oncolytic virus therapy. Oncolytic virus therapy may be combined with another therapy such that its effects on the immune system may synergize with the other therapy. Mathematical modeling plays an important role in optimizing this synergy in preclinical experiments minimizing efforts to translate into clinical trials. For the use of Schwarz measles virus on pancreatic cancer, data was collected from real time cell analysis (RTCA), which measures cytotoxicity via the adherence of live cells. Simultaneous modeling of human pancreatic adenocarcinoma (HPAC) cell growth +/- single-dose of measles resulted in fits where $R^2 > 0.9$. These models were then used to create a multiple-dose measles model, and RTCA experiments were performed for validation. Model development of HPAC treated with the Schwarz strain of measles is presented.
SMB 2017 Contributed Talk Abstract
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B. Title And Abstract:

Title: Temporal Dynamics of Macrophages Plasticity in the Bone Microenvironment

Abstract: Prostate to bone metastasis remains the main cause of death for patients with prostate cancer. The ability of prostate cancer cells to interact with bone resident cells and imbalance the bone cycle result in painful osteogenic lesions. Despite the improving understanding of this bone vicious cycle and the subsequent developed treatments, prostate to bone metastasis remains incurable in most of the cases. However, some aspects of the bone microenvironment relevant to metastases have been poorly studied so far. An increasingly relevant example of this are macrophages, which are a particularly common immune cell type in the bones. Recent studies shed light on their role during bone inflammation, repair and remodeling and suggested them as important intermediate players between osteoblasts and osteoclasts orchestrating multiple steps of bone turnover. Moreover, many studies provided evidence for context-dependent pro and antitumoral effects of tumor-associated macrophages. Here we propose an interdisciplinary approach combining in silico and in vivo models to understand more about the largely unexplored role of macrophages in normal bone remodeling and cancer-bone interactions. The ordinary differential equation-based model describes coupled population dynamics of diversely polarized macrophages and bone resident cells with biological assumptions based on a substantial literature review of the bone repair biology. Whereas some of the parameters of the model were fixed to physiologically relevant or experimentally measured values, other ones were calibrated to the in vivo data. According to the observations, the injury is followed by an increase in inflammatory macrophages and a decrease in anti-inflammatory macrophages, and the ODE model describing plasticity between macrophage subtypes is able to recapitulate the complex dynamical behavior of macrophages that is observed in vivo during bone repair. This experimentally validated model is then used to investigate the cellular interactions occurring when a prostate cancer cell is introduced in the bone microenvironment.
SMB 2017 Contributed Talk Abstract

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B. Title and abstract
A model of natural selection predicts treatment resistance in prostate cancer

Standard of care treatment for recurrent and advanced prostate cancer includes chemical castration. Inevitably, however, such treatment results in hormone-refractory tumors with dire prognosis. Clearly, a predictive mathematical model of this process would greatly improve our understanding and ability to mitigate castration resistance in this tumor. Here I develop an adaptive dynamics model of androgen-ablation therapy and show that it predicts progression of treatment resistance in a significant subset of prostate cancer patients. The model assumes that castration resistance evolves due to natural selection on androgen receptor (AR) expression. Formulation and parameterization of the model was completed based on a sample of 25 patients treated with intermittent androgen ablation therapy. The model was then used to predict PSA dynamics in an independent set of 30 patients from the same clinical study. Predictions were reasonably accurate typically for one cycle, and for some patients up to 4 cycles. However, there were significant exceptions—in some cases the model exhibited no predictive power. These observations are consistent with the conclusion that the model accurately reflects castration resistance arising via natural selection acting on AR expression, but fails for cases in which resistance is caused by a different mechanism, like “outlaw” or AR bypass pathways. This modeling approach therefore may provide a noninvasive method to identify emerging resistance mechanisms in nascent hormone-refractory tumors and to plan treatment to delay development of castration resistance.
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B Title and Abstract

Title: Optimal chemotherapy scheduling based on a pair of collaterally sensitive drugs

Abstract:
Despite major strides in the treatment of cancer, the development of drug resistance remains a major hurdle. To address this issue, researchers have proposed sequential drug therapies with which the resistance developed by a previous drug can be relieved by the next one, a concept called collateral sensitivity.

Inspired by such studies, we develop multiscale dynamical models and study the effect of sequential chemotherapy utilising a pair of drugs (A-type, B-type) switched in turn within the therapy schedule. An important assumption in our model is that a tumor is comprised by two types of cell groups, A-resistant and B-resistant, each of which is resistant to the indicated drug and sensitive to the other.

Based on a population based ODE system, we determined that the optimal treatment strategy consists of two stages: (i) the initial stage in which a chosen better drug is utilised until a specific time point, $T$, and afterward; (ii) a combination of the two drugs switched in turn with a definite ratio in duration, $k$. Of note, we prove that the initial period, in which the first drug is administered, $T$, is shorter than the period in which remains effective, contrary to clinical intuition.

Beyond our analytic results, we explore an individual based stochastic model and present the distribution of extinction times for the classes of solutions found. Taken together, our results suggest opportunities to improve chemotherapy scheduling in clinical oncology.
CS10: Epidemiology Strategies

Wednesday, July 19
10:30–12:30
Bonneville Room

List of Talks:

- *A computational model to evaluate outcomes of various vaccine strategies*
  Marek Laskowski, Yanyu Xiao*, Nathalie Charland, Seyed Moghadas

- *Efficient mitigation of multi-drug resistant organisms in healthcare networks*

- *Modeling Intervention Policies for Chlamydia Using Stochastic Network Simulations*
  Asma Azizi*, James Mac Hyman

- *An exact approach to calibrating infectious disease models to surveillance data: the case of HIV and HSV-2*
  David Gerberry*

- *Guidelines overestimate within-hospital transmission of Clostridium difficile*
  Angus McLure*, Archie C. A. Clements, Martyn Kirk, Kathryn Glass

- *A model of the effects of antibiotics exposure on C. diff in a hospital setting*
  Christopher Mitchell*, Damon Toth
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B. Title: A computational model to evaluate outcomes of various vaccine strategies.
Abstract: In this work, we investigated the impact of early vaccination on age-specific attack rates and evaluate the outcomes of different vaccination strategies that are influenced by the level of single or two-dose vaccine-induced protections. We developed and parameterized an individual-based model for two population demographics of urban and remote areas in Canada. Our results demonstrate that there is a time period before and after the onset of epidemic, during which the outcomes of vaccination strategies may differ significantly and are highly influenced by demographic characteristics.
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Title: Efficient mitigation of multi-drug resistant organisms in healthcare networks

Abstract:
Multi-drug resistant organisms (MDROs) pose a major public health threat and have been increasingly targeted for efforts to decrease transmissions and infections in healthcare facilities. MDRO outbreaks can occur at a regional level across networks of hospitals and long-term care facilities that exchange patients. Designing interventions to interrupt MDRO spread might be more efficiently designed when informed by regional epidemiological dynamics, but these are difficult to study empirically. We designed a detailed mathematical model of patients in a regional network of 10 healthcare facilities including 1 long-term acute care hospital (LTACH), 3 short-stay acute care hospitals (ACHs) and 6 nursing homes (NHs). We have calibrated the model to achieve realistic patient flow and transmission and detection rates for multiple high-priority MDROs, and used intervention simulations to study the regional benefits of strategically targeted efforts. Our results show promising advantages to improved inter-facility coordination and communication when reacting to a new regional outbreak, but also demonstrate that funneling resources into transmission prevention at the single LTACH can be a highly efficient strategy from the regional perspective.
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• B. Title And Abstract:
Modeling Intervention Policies for Chlamydia Using Stochastic Network Simulations
Chlamydia trachomatis (Ct) is the most commonly reported STI in the United States with an estimated 1.7 million infections per year. According to the United States Add health there is a 4.9% prevalence of Ct among 18-26 years old sexually active individuals. There is a high prevalence of Ct rate among African American (AA) sexually active people aged 15-25 reside in New Orleans, 8% among men and 12% among women. We create and analyze an individual network-based model for the spread of Chlamydia trachomatis, Ct, in New Orleans. Based on partnership distribution, we made a bipartite sexual network for men and women. We Implemented a MCMC stochastic susceptible-infected-susceptible (SIS) Ct transmission model on this network and identified model parameters that agree with the known Ct incidence in New Orleans. We use the model to quantify the effectiveness of different intervention measures: Partner notification strategies, screening and rescreening of various subgroups, and the effect of condom use are compared in the model.
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2 Title and abstract

Title:
An exact approach to calibrating infectious disease models to surveillance data: the case of HIV and HSV-2

Abstract:

When mathematical models of infectious diseases are used to inform health policy, an important first step is often to calibrate a model to disease surveillance data. While frequently overlooked, the calibration process is nontrivial at best and can be inefficient, poorly communicated and a major hurdle to the overall reproducibility of modeling results.

In this work, we describe a general approach to calibrating infectious disease models to surveillance data. The technique is able to match surveillance data to high accuracy in a very efficient manner as it is based on the Newton-Raphson method for solving nonlinear systems. To demonstrate its robustness, we use the calibration technique on multiple models for the interacting dynamics of HIV and HSV-2.
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B. Title and Abstract
Guidelines overestimate within-hospital transmission of Clostridium difficile

Clostridium difficile is the leading cause of hospital-associated gastrointestinal infections in the developed world. Hospitalised patients that develop Clostridium difficile infections may have acquired the infection during their hospitalisation or prior to admission. Current guidelines for Clostridium difficile infections (CDIs) classify all cases with the onset of symptoms ≥2 days after hospital admission as hospital-acquired. However, the incubation period for C. difficile is often much longer than two days which may result in significant misclassification.

We used a stochastic, compartmental model of C. difficile transmission in an endemic healthcare setting to assess the current guidelines for classifying the origin of CDI. Our model captured asymptomatic colonisation, immune responses and the disruption of protective gut flora caused by exposure to antibiotics. We calculated the distribution of the time from admission to onset of symptoms for CDIs acquired during the current hospitalisation and CDIs acquired prior to the current hospitalisation. We conducted sensitivity analyses to compare our base scenario with a broad range of plausible scenarios.

In our base scenario, the recommended two-day classification had good sensitivity but poor specificity to identify CDIs acquired in the current hospitalisation, overestimating their incidence by nearly 100%. A six-day cut-off accurately estimated the incidence of CDIs acquired during the current hospitalisation and CDIs acquired prior to the current hospitalisation. In the sensitivity analysis, a two-day cut-off consistently overestimated the incidence of CDIs acquired in the current hospitalisation, especially in settings with low within-hospital transmission.

The recommended two-day cut-off systematically overestimates the proportion of CDIs that are acquired in the current hospitalisation and underestimates the proportion that are acquired prior to admission. This may make policymakers overly optimistic about the potential benefits of interventions that only address within-hospital transmission. A cut-off of five or more days is more appropriate for a wide range of healthcare settings.
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B. Title: A model of the effects of antibiotics exposure on C. diff in a hospital setting

*Clostridium difficile* infection (CDI) is a frequent cause of diarrhea in healthcare facilities, sometimes leading to life-threatening colon inflammation. CDI typically occurs after exposure to certain antibiotics that can disrupt the normally protective gut microbiota, suggesting that reducing unnecessary antibiotic exposure can reduce CDI. Projected impacts of antibiotic stewardship interventions on CDI vary due to uncertain mechanisms of interaction between antibiotics and CDI dynamics in healthcare settings. We designed a mathematical model based on detailed hospital inpatient antibiotic prescribing data to explore two nuanced aspects of these dynamics: the effect of antibiotics on acquisition of colonization with *Clostridium difficile* vs. progression to CDI among those already colonized, and the effect of certain antibiotics during a course of exposure vs. after the course is finished. The model shows that 1) assuming effects on acquisition vs. progression has little effect on projections for inpatient CDI reduction, but does affect projected reduction of carriage among discharged patients; and 2) reducing the rate of starting new antibiotic courses decreases projected CDI, but reducing the duration of courses increases CDI under plausible assumptions about antibiotic effect timing.
CS11: Fluids
Thursday, July 20
10:30–12:30
City Creek Room

List of Talks:

- Effects of Fibrinolytic Inhibitors on Enzyme Diffusion and Clot Degradation
  Brittany Bannish*, James Keener, Aaron Fogelson

- Measuring the Speed of Biochemical Reactions
  Ryan Evans*, Anthony Kearsley, David A. Edwards, Arvind Balijepalli

- Swimming performance, resonance, and shape evolution in heaving flexible panels
  Alexander Hoover*, Ricardo Cortez, Eric Tytell, Lisa Fauci

- Ascent of Sap in Trees: the forward problem and the inverse problem
  Bebart Janbek*, John Stockie

- Polymorphic transformation of rotating bacterial flagella in a viscous fluid
  Sookkyung Lim*

- Hydrodynamic sensing and predator localization by free-swimming organisms
  Daisuke Takagi*, Daniel Hartline
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Aaron Fogelson, 155 S 1400 E, Salt Lake City, UT, 84112, fogelson@math.utah.edu

B. Title: Effects of Fibrinolytic Inhibitors on Enzyme Diffusion and Clot Degradation

Abstract: Understanding how blood clots degrade is important from both physiological and clinical standpoints. We develop a stochastic multiscale model of fibrinolysis to study how the presence of fibrinolytic inhibitors affects the progression of degradation. Specifically, we study the direct inhibitor α2-antiplasmin and the indirect inhibitor thrombin-activatable fibrinolysis inhibitor (TAFI). We show that the presence of these inhibitors affects the amount of plasmin (the main fibrinolytic enzyme) produced and how this reduction in plasmin slows the effective diffusion of other important enzymes through the clot. Results of this work have implications for stroke drug development.
Measuring the Speed of Biochemical Reactions

Ryan Evans\textsuperscript{1,*}, Anthony Kearsley\textsuperscript{1,**}, David A. Edwards\textsuperscript{2}, Arvind Balijepalli\textsuperscript{3}

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Primary Area: Fluids
Secondary Area: Dynamical Systems

Abstract

Many biochemical reactions involve a stream of chemical reactants flowing through a fluid-filled volume, over a surface to which receptors are confined. Such surface-volume reactions occur during blood clotting, drug-protein interactions, and DNA-damage repair. Scientists measure reaction rate constants associated with these reactions using optical biosensors: an instrument in which reactants are convected through a flow-cell, over a surface to which other reactants are immobilized.

Scientists currently study biosensor experiments which involve multiple interacting components on the sensor surface. We discuss a partial differential equation model for multiple-component reactions in optical biosensors. Thanks to high Peclet number flow, this model reduces to a set of nonlinear integrodifferential equations for the reacting species concentrations, which in turn reduces to a set of ordinary differential equations which can be used to measure rate constants using biosensor data. We conclude by discussing recent developments on a related problem concerning instruments involved in creating personalized medicine.
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B Title: Swimming performance, resonance, and shape evolution in heaving flexible panels

Abstract: Many animals that swim or fly use their body to accelerate the fluid around them, transferring momentum from their flexible bodies and appendages to the surrounding fluid. The emergent kinematics from this transfer are a result of the coupling between the fluid and the active and passive material properties of the flexible body or appendages. Here we present a computational studies of a three-dimensional flexible panel that is heaved sinusoidally at its leading edge in an incompressible, viscous fluid. These high-fidelity numerical simulations enable us to examine the role of resonance, fluid forces, and the emergent panel shape deformations in propulsive performance. Varying both the passive material properties and the heaving frequency of the panel, we find that local peaks in trailing edge amplitude and forward swimming speed are determined by a dimensionless quantity, the effective flexibility, that arises from the Euler-Bernoulli beam equation. Modal decompositions of panel deflections reveal that the strength of each mode is related to the effective flexibility, and that local peaks in the swimming speed and trailing edge amplitude correspond to peaks in the contributions of different modes. We find that panels of different material properties that are actuated so that their effective flexibilities are closely matched have modal contributions that evolve similarly over the phase of the heaving cycle and exhibit strong agreement in dominant vortex structures generated by the panel deflections over the heaving cycle.
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B. Title and Abstract
Title:
Ascent of Sap in Trees: the forward problem and the inverse problem

Abstract:
The ascent of water in trees, from the roots to the leaves, for vertical distances that may reach more than a 100 meters, is a problem that has puzzled plant physiologists for a long time. The story starts from the leaves, with evaporation from the leaves causing the water to recede into the interstitial spaces in the leaves cells, and thus create high interfacial tension forces, that are transmitted to the rest of the tree vascular system, and are able to pull the water from the roots. Various models have been developed to capture the different aspects of this flow, for use in environmental studies, forestry and agriculture. Though these models replicate some observed experimental findings, they are mostly computational models, that lack mathematical generality, and not much mathematical analyses has been performed on these models. We propose a 3D porous medium model, that extends and generalizes previous 1D models, and captures the radial component and the radial variation in the trunk sap velocity. Through asymptotic and numerical analysis, we solve the forward problem of determining the sap velocity given the transpiration function from the leaves. This gives us a new insight into the observed radial variations in the vertical velocity in the case of high anisotropic hydraulic conductivity, and furnishes the way for solving the more interesting and practical inverse problem of determining the transpiration function given discrete measurements of the sap velocity. For this purpose, we use the velocity formulas obtained when solving the forward problem, and propose a variational formulation to recover the spatial and temporal variations of the transpiration function, that tolerates errors in the velocity measurement. We also propose a way to parametrize the model through direct measurement of its dimensionless parameters.
A. Authors

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B. Title and Abstract

Title: Polymorphic transformation of rotating bacterial flagella in a viscous fluid
Abstract: Bacteria such as E. coli utilize their helical flagella to swim in an aqueous environment. Each helical flagellum is equipped with a rotary motor that can turn either clockwise or counterclockwise and it goes through polymorphic transformations in that the flagellum changes in helical pitch, radius, and handedness. We present a mathematical model of a single flagellum described by Kirchhoff rod model immersed in a Stokes flow and investigate two mechanisms by which polymorphic transformation can occur, as observed in experiments, either by (1) reversing the motor rotation and (2) anchoring one end of the flagellum under the steady flow. The detailed dynamics of the helical flagellum interacting with a viscous fluid and comparisons with experimental results will be presented. This work is in collaboration with W. Ko, B. Griffith, Y. Kim, C.S. Peskin, H. Berg, and W. Lee.
SMB 2017 Contributed Talk Abstract

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B. Title And Abstract

Title: Hydrodynamic sensing and predator localization by free-swimming organisms

Abstract: The sensory world of free-swimming animals differs radically from that of substrate-dwelling animals. Those carried with the surrounding water and unable to detect its bulk flow have a harder task of detecting objects causing the flow, such as an attacking predator. Cues from local water deformations are nevertheless available to such animals, and reconstructing possible causes of the signals is a timely unresolved problem at the interface of mathematics and biology. We present a theory that clarifies what information is contained in disturbances generated by an attacking predator, and we apply it to planktonic copepods that have mechanosensory hairs deployed in a one-dimensional array along a pair of antennules. The theory reveals the presence of “blind spots”, potential ambiguities in resolving from which of two sides a predator attacks, and whether it generates a bow wave or suction. Our results show that free-swimming animals perceive an intriguingly ambiguous world, yet they may nonetheless extract sufficient information on the location and imminence of the attack to make informed life-saving decisions in their behavioral reactions.
CS12: Epidemiology Dynamics
Thursday, July 20, 10:30–12:30, Officer’s Club East

List of Talks:

• *Virulence Evolution of Toxoplasma gondii Strain within a Multi-host System*
  Wen Jiang*, Mengyue Wang, Lei Yang

• *Multi-Patch and Multi-Group Epidemic Models: A New Framework*
  Derdei Bichara*, Abderrahman Iggidr

• *Continuous and Discrete SIR Models with Spatial Distributions*
  Seong-Hun Paeng, Jonggul Lee*

• *A mathematical model for the transmission of Louse-Borne Relapsing Fever*
  Aluod Alsheri*, Stephen A. Gourley

• *How honeybee drift affects apiary disease burden*
  Carly Rozins*, Lewis Bartlett, Mike Boots

• *Modeling Differential Transmission Characteristics of Whitefly-Transmitted Cassava Viruses*
  Jing Li*, James P Legg, Yang Kuang, Jo Ann Lee, Ariel Cintron-Arias, Ilsa Bosque-Perez, Simon Jeremiah, Geoffrey Okao-Okuja, Suzanne Lenhart

• *Mathematical models of Emerging Infectious Diseases in the Republic of Korea*
  Eunok Jung*, Jonggul Lee
Virulence Evolution of *Toxoplasma gondii* Strain within a Multi-host System

Wen Jiang\textsuperscript{1,2,*}, Mengyue Wang, Lei Yang\textsuperscript{1,2}

(1. Department of Mechanics, Huazhong University of Science & Technology, Wuhan, China; 2. Hubei Key Laboratory for Engineering Structural Analysis and Safety Assessment, Wuhan, China)

**Abstract:** The successfuleness of *Toxoplasma gondii* (*T. gondii*) is closely related to its complex and flexible life cycle including both sexual and asexual transmission, which enables it to infect all mammals and birds. It is expected that the parasite is genetically diverse due to its biological and epidemiological diversity; however, this genetic diversity can only be found in some areas while, in most areas of the world, there is only one or several types of *T. gondii* strains overwhelmingly dominant. The previous research by the authors indicates that this regional distribution difference of *T. gondii*, which can be regarded as a kind of evolutionary bifurcation, might be explained from the perspective of evolution of *T. gondii* strain. The present research is to extend that investigation by involving the complete life cycle of *T. gondii* and, most importantly, considering different kinds of hosts of *T. gondii*. The authors build up an evolutionary dynamics model on the virulence of *T. gondii* strain considering three main transmission routes, i.e., direct contact, indirect infection from the environment and vertical transmission from mother to child, as well as different kinds of hosts, i.e., definite hosts and intermediate hosts w/o predation with definite hosts. Evolution of the virulence of the strain is investigated by introducing mutant strain. The evolutionarily singular strategy, which is the virulence at the evolutionarily equilibrium point, can be reached when the basic reproduction number of that mutant system is a maxima. The analysis on the stability of those evolutionarily singular strategies can tell us the evolutionary scenarios of *T. gondii*. In addition, by varying the associated parameters, one can change the relative strength of direct, environmental and vertical transmission. Based on the analyses within this framework, one can figure out that the a small convergence stable singularity can be obtained when direct transmission dominates, which implies that only avirulent strain can dominant in the areas where *T. gondii* is primarily transmitted directly through the ingestion of undercooked meat harbouring tissue cysts in city areas, e.g., Europe and North America. On the other hand, a branching point can be found when indirect transmission dominates, i.e., through the feeding of contaminated food or water indirectly from the environment polluted by the free parasites spread by cats in undeveloped areas without the influence of human activities, e.g., Central and South America. Furthermore, one can find out that the variation of parameters associated with predator-prey relation between the hosts and vertical transmission can greatly change the evolutionary scenarios of the strain, which indicate that further investigation on those two factors is necessary to determine the true picture of the virulence evolution of *T. gondii*.

**Key words:** Toxoplasmosis; evolutionary bifurcation; invasion dynamics; multi hosts
Multi-Patch and Multi-Group Epidemic Models: A New Framework

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March 30, 2017

**Abstract:** We develop a multi-patch and multi-group model that captures the dynamics of an infectious disease when the host is structured into an arbitrary number of groups and interacts into an arbitrary number of patches where the infection takes place. In this framework, we model host mobility that depends on its epidemiological status, by a Lagrangian approach. This framework is applied to a general SEIRS model and the basic reproduction number $R_0$ is derived. The effects of heterogeneity in groups, patches and mobility patterns on $R_0$ and disease prevalence are explored. Our results show that for a fixed number of groups, the basic reproduction number increases with respect to the number of patches and the host mobility patterns. Moreover, when the mobility matrix of susceptible individuals is of rank one, the basic reproduction number is explicitly determined and was found to be independent of the latter. The cases where mobility matrices are of rank one capture important modeling scenarios. Additionally, we study the global analysis of equilibria for some special cases. Numerical simulations are carried out to showcase the ramifications of mobility pattern matrices on disease prevalence and basic reproduction number.
SMB 2017 Contributed Talk Abstract

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B. Title and Abstract
Title (80 characters maximum)
Continuous and Discrete SIR Models with Spatial Distributions

Abstract (keep it reasonably short, definitely fits on page)
The SIR model is a basic epidemic model that classifies a population into three subgroups: susceptible $S$, infected $I$, and removed $R$. This model does not take into consideration the spatial distribution of each subgroup, but considers the total number of individuals belonging to each subgroup. There are many variants of the SIR model. For studying the spatial distribution, stochastic processes have often been introduced to describe the dispersion of individuals. Such assumptions do not seem to be applicable to humans, because almost everyone moves within a small fixed radius in practice. Even if individuals do not disperse, the transmission of disease occurs. In this paper, we do not assume the dispersion of individuals, and instead use the infectious radius reflecting the infection intensity. Then, we propose simple continuous and discrete SIR models that show spatial distributions. The results of our simulations show that the propagation speed and size of an epidemic depend on the population density and the infectious radius.
Ahuod Alsheri¹ (presenter) and Stephen A. Gourley²

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**A mathematical model for the transmission of Louse-Borne Relapsing Fever**

**Abstract.** We present a detailed derivation and analysis of a model consisting of seven coupled delay differential equations for Louse Borne Relapsing Fever (LBRF), a disease transmitted from human to human by the body louse *Pediculus humanus humanus*. Delays model the latency stages of LBFR in humans and lice, which vary in duration from individual to individual, and are therefore modelled using distributed delays with relatively general kernels. A particular feature of the transmission of LBFR to a human is that it involves the death of the louse, usually by crushing which has the effect of releasing the infected body fluids of the dead louse onto the host’s skin. Careful attention is paid to this aspect. We obtain results on existence, positivity, boundedness, linear and nonlinear stability, and persistence. We also derive a basic reproduction number $R_0$ for the model and discuss its dependence on the model parameters. Our analysis of the model suggests that effective louse control without crushing should be the best strategy for LBFR eradication. We conclude that simple measures and precautions should, in general, be sufficient to facilitate disease eradication.

**Key words:** Louse Borne Relapsing Fever; Vector-Borne Disease; Epidemic; Delay; Stability; Basic Reproduction Number.
A) Carly Rozins*, Lewis Bartlett, Mike Boots
* presenting author

B) Title: How honeybee drift affects apiary disease burden.

Abstract: Within an apiary, honeybee hives are commonly arranged in a generalization of one of three spatial arrangements: array, circular or lattice. It is well established that honeybee drifting between hives is influenced by the spatial arrangement of hives within the apiary. What is less known, however, is the extent to which drifting contributes to the spread of pathogens, such as the deformed wing virus and its vector, Varroa destructor. To answer this question, we derive an apiary-wide epidemiological model which tracks drifting and the spread of disease between neighboring hives. We investigate the three most common hive arrangements and establish to what extent hive arrangement contributes to the vulnerability of a disease outbreak. As disease is endemic, we also establish the expected degree of disease burden within each hive in the apiary.
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B. Title and Abstract

Title  Modeling Differential Transmission Characteristics of Whitefly-Transmitted Cassava Viruses

Abstract

Cassava mosaic geminiviruses (CMGs) and Cassava brown streak viruses (CBSVs) have been associated with region wide spread of a dual pandemic of cassava mosaic disease (CMD) and cassava brown streak disease (CBSD). The whitefly, Bemisia tabaci, is responsible for semi-persistently transmitting CMGs for CMD and persistently transmitting CBSVs for CBSD in East and Central Africa. We compared local transmission characteristics of both viruses using modeling techniques, to derive novel insights into factors driving these epidemics. A system of five ordinary differential equations was formulated with mechanisms to illustrate differences between transmission effects of CMGs and CBSVs on cassava plants at the field level. Field data for model fitting were obtained from experimental trials planted with CMD-susceptible and CMD-resistant cassava varieties (both susceptible to CBSD) in Ukerere Island in north-western Tanzania and at Namulonge, in south-central Uganda. Our simulations show that these models not only fit the field data well, with biologically meaningful parameter estimates, but additionally they also capture the differences between the two types of viral infections: CMGs and CBSVs. These data-validated models are also employed to simulate infection dynamics subject to various starting plant infection levels and whitefly abundance values. The models generated here will be building blocks for models with larger spatial features at the regional level with multiple fields, which will ultimately serve as tools aiding disease management decisions. Modeling results may be relevant to other crop systems where virus groups with similarly contrasting transmission characteristics occur.
SMB 2017 Contributed Talk Abstract

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B. Title and Abstract
Emerging infectious diseases have long been recognized as a continuous, inevitable, unpredictable threat to the global public health. Hence, understanding the underlying dynamics why they spread and what causes epidemics give key ideas of intervention strategies. in this talk, we will present the development of new mathematical models for the spread of two emerging infectious diseases in the Republic of Korea, 2009 A/H1N1 pandemic and 2015 Middle East respiratory syndrome outbreak, and the effects of public health intervention in the early stage of the outbreaks. Using the laboratory-confirmed case data, the spreading dynamics of transmission is investigated. Results in this work suggest that heterogeneity plays a key role in the spread of two emerging infectious diseases in the Republic of Korea. Our findings show that interventions in the early stage of the outbreak could reduce the epidemic size up to 19% for the 2009 pandemic influenza, and up to 80% for the 2015 MERS outbreak
List of Talks:

- *Stochastic Modelling of the Wnt Signalling Pathway*
  James Cavallo*, Mark Flegg

- *Sufficient Conditions for Ergodicity of Stochastic Reaction Networks and Mixing Times*
  Jinsu Kim*, David Anderson

- *Mechanisms of noise-induced oscillation in models of gene regulatory networks*
  Yen Ting Lin*, Nicolas E. Buchler

- *Modeling sorption of trace-elements in multispecies biofilms*
  B D’Acuntoa*, L Frunzoa, MR Matteia

- *Multi-scale modeling of biofilm growth in porous medium reactors*
  Harry Gaebler*, Hermann Eberl
Authors

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Title

Stochastic Modelling of the Wnt Signalling Pathway

Abstract

The Wnt signalling pathway is a pathway for normal developmental and homeostatic cellular behavior. It can influence cell proliferation, differentiation and other characteristics such as polarization. Mutations and abnormalities in this pathway are known to be involved in diseases such as cancer. To date, mathematical models that explain and predict the cellular response to Wnt stimuli are restricted to deterministic ODE models for protein concentrations. These types of models however, may be restrictive since Axin (an influential negative regulator of the pathway) may exist at small concentrations subjecting the system to strong intrinsic noise. Furthermore, it has been shown that Wnt signalling may elicit feedback in the form of Axin2 synthesis. Thus, we focus our work on the translation of accepted canonical Wnt signalling models into a stochastic model. We address a major challenge in constructing a stochastic model of a signalling pathway (where noise is modelled intrinsically). Rapid enzyme reactions, which are ubiquitous in cell signalling, can be difficult to model in an individual molecule-based simulation (such as in a Smoluchowski framework) due to a break down of the assumptions used to describe the chemical interaction. Using ODEs, these rapid interactions can be easily analyzed using a pseudo-steady state approximation which results effectively in non-linear or high order reactions. We develop the Smoluchowski individual molecule-based framework to include reversible high order reactions in order to construct a stochastic model of the Wnt signalling pathway.
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B. Title: Sufficient Conditions for Ergodicity of Stochastic Reaction Networks and Mixing Times.
Abstract: Reaction networks are graphical configurations that can be used to describe biological interaction networks. If the abundances of the constituent species of the system are low, we can model the dynamics of species counts in a jump by jump fashion as a continuous time Markov chain. In this talk, we will mainly focus on which conditions of the graph imply ergodicity (existence of a stationary distribution) for the associated continuous time Markov chain. I will also present results related to their mixing times, which give the time required for the distribution of the continuous time Markov chain to get close to the stationary distribution.
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Title and Abstract

Title: Mechanisms of noise-induced oscillation in models of gene regulatory networks

Abstract:

Many mathematical models describing the dynamics of gene regulatory networks (GRN) governing circadian rhythm have been proposed in the past two decades. Because the interacting chemical species—promoter sites on genes, mRNA, and transcriptional factor—are fundamentally discrete chemical molecules, it is inevitable to introduce the intrinsic noise in detailed model descriptions. Several studies have concluded that the intrinsic noise in these chemical reaction networks can facilitate oscillatory dynamics that are otherwise not possible in the deterministic descriptions.

In this talk, we first present an idealised model which encapsulates three significantly different mechanisms to induce oscillatory dynamics by intrinsic noise. We present the corresponding mathematical and analytical methods to analyse each of the mechanisms. While the methods to analyse the first two of these mechanisms have been developed almost completely, the third mechanism which utilises slow binding/unbinding events between the transcriptional factors and the promoter sites has not been understood thoroughly. We propose an mathematical framework using the piecewise deterministic Markov process to systematically analyse the stochastic process, quantify the variability of the periods of the cycles, and identify the predominant source of uncertainties. Finally, we present quantitative evidence of the manifestation of each mechanism in published more complex models. The results of parallel analyses on these more complicated models will also be presented.

Our study provides the mechanistic insights of these noise-induced oscillations. The fact that the idealised model captures all of these mechanisms suggests that (1) this model merits more rigorous mathematical analyses, and (2) the model serves as a computational platform to test evolutionary hypotheses in the future. Finally, our proposed framework using piecewise deterministic Markov process to analyse the dynamics with slow binding/unbinding events merits more investigations, as more experiments revealed that this could be a biologically relevant parameter regime.
Modeling sorption of trace-elements in multispecies biofilms

B D’Acunto\textsuperscript{a}, L Frunzo\textsuperscript{a,b}, MR Mattei\textsuperscript{a}

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The presentation will concern a mathematical model for micro-elements sorption in multispecies biofilms, based on a continuum approach and mass conservation principles. Diffusion of contaminants within the biofilm is described using a diffusion-reaction equation. Binding sites formation and occupation are modeled by two systems of hyperbolic partial differential equations mutually connected through the two growth rate terms. The model is completed with a system of hyperbolic equations governing the microbial species growth within the biofilm, a system of parabolic equations for substrates diffusion and reaction and a nonlinear ordinary differential equation describing the free boundary evolution.

The complete model takes the following form:

$$\frac{\partial X_i}{\partial t} + \frac{\partial}{\partial z}(uX_i) = \rho_i r_{M,i}(z,t,X,S,\mu), \quad i = 1, \ldots, n, \quad 0 \leq z \leq L(t), \quad t > 0,$$

$$\frac{\partial u}{\partial z} = \sum_{i=1}^{n} r_{M,i}(z,t,X,S,\mu), \quad 0 < z \leq L(t), \quad t \geq 0,$$

$$\dot{L}(t) = u(L(t),t) + \sigma_a(t) - \sigma_d(L(t)), \quad t > 0,$$

$$\frac{\partial}{\partial t} \left( u \vartheta_i \right) + \frac{\partial}{\partial z} \left( u \vartheta_i \right) = r_{M,i}(z,t,X,S,\mu) - r_{D,i}(z,t,\mu,\vartheta,\bar{\vartheta}_i), \quad i = 1, \ldots, n, \quad 0 \leq z \leq L(t), \quad t > 0,$$

$$\frac{\partial}{\partial t} \left( u \bar{\vartheta}_i \right) + \frac{\partial}{\partial z} \left( u \bar{\vartheta}_i \right) = r_{D,i}(z,t,\mu,\vartheta,\bar{\vartheta}_i), \quad i = 1, \ldots, n, \quad 0 \leq z \leq L(t), \quad t > 0,$$

$$\frac{\partial}{\partial t} \left( D_k \frac{\partial \mu_i}{\partial z} \right) = -Y_{ADS} N_i r_{D,i}(z,t,\mu,\vartheta,\bar{\vartheta}_i), \quad i = 1, \ldots, n, \quad 0 \leq z \leq L(t), \quad t > 0,$$

$$\frac{\partial S_j}{\partial t} - \frac{\partial}{\partial z} \left( D_{S,j} \frac{\partial S_j}{\partial z} \right) = r_{S,j}(z,t,X,S,\mu), \quad j = 1, \ldots, m, \quad 0 < z < L(t), \quad t > 0,$$

The Mathematical Modelling of three real special cases will be presented. The first describes the dynamics of a free sorbent component diffusing and reacting in a multispecies biofilm. In the second illustrative case, the fate of two different trace-elements is modelled. In the third case the microbial growth is directly related to the contaminant concentration.
Authors:

Harry Gaebler (presenter)
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Title And Abstract:

Title: Multi-scale modeling of biofilm growth in porous medium reactors

Abstract: We derive a multi-scale model for biofilm formation in a porous medium reactor. The starting point is the traditional mesoscopic one-dimensional Wanner-Gujer biofilm model. Mesoscopic processes included in the model are hydrodynamics and transport of substrates in the reactor, biofilm and planktonic bacteria growth in the pore space through consumption of a single, non-reproducing growth limiting substrate, attachment of planktonic cells to the biofilm, detachment of biofilm cells, and cell lysis. The mesoscopic equations are up-scaled from the biofilm scale to the reactor scale, yielding a stiff system of quasilinear hyperbolic balance laws, which are studied numerically. We investigate the role of planktonic bacteria and the effect attachment has on reactor performance, with an application to clay filters for water purification.
CS14: Ecological Dynamics

Thursday, July 20
3:00–5:00
City Creek Room

List of Talks:

- *Leading indicators of extinction in a spatially-extended ecological system*
  Suzanne M. O’Regan*

- *Population dynamics in a fragmented landscape with small patches: The Bodie pika*
  Sabrina F. Jones*, John D. Nagy

- *Anomalous invasion speeds in highly polymorphic populations*
  Vincent A. Keenan*, Stephen J. Cornell

- *Can trapping invasive crayfish help to save California newts?*
  Courtney Davis*, Timothy Lucas, William Milligan

- *Neutral Genetic Patterns for Expanding Populations*
  Nathan G. Marculis* Roger Lui, Mark A. Lewis

- *Tipping points in resource abundance drives changes in community structure*
  Seth Haney*, Adam Siepielski

- *Spatial scales of alternative stable states in demographically open systems*
  Vadim A. Karatayev*, Marissa L. Baskett

- *Optimal fishery harvesting modeling the effects of habitat degradation*
  Michael R. Kelly, Jr.*, Suzanne Lenhart, Michael Neubert
A. Authors

Name: Suzanne M. O'Regan¹,² (Presenter)

Address: ¹National Institute of Mathematical and Biological Synthesis, University of Tennessee, USA ²North Carolina A&T State University, Greensboro, NC, USA

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B. Title and Abstract

Leading indicators of extinction in a spatially-extended ecological system

Anticipating critical transitions in spatially extended systems is a key topic of interest to ecologists. Gradually declining metapopulations are an important example of a spatially extended biological system that may exhibit a critical transition. Theory for spatially extended systems approaching extinction that accounts for environmental stochasticity and coupling is currently lacking. Here, I develop spatially implicit two-patch models with additive and multiplicative forms of environmental stochasticity that are slowly forced through population collapse, through changing environmental conditions. I derive patch-specific expressions for candidate indicators of extinction and test their performance via a simulation study. Coupling and spatial heterogeneities decrease the magnitude of the proposed indicators in coupled populations relative to isolated populations, and the noise regime and the degree of coupling together determine trends in summary statistics. This theory may be readily applied to other spatially extended ecological systems, such as coupled infectious disease systems on the verge of elimination.
SMB 2017 Contributed Talk Abstract

A. Author

Sabrina F. Jones\textsuperscript{1,2}, John D. Nagy\textsuperscript{2,3}

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\textsuperscript{3}Department of Life Sciences, Scottsdale Community College, Scottsdale, AZ 85256-2626 USA

B. Title and abstract

Population dynamics in a fragmented landscape with small patches: The Bodie pikas

A population of American pikas (\textit{Ochotona princeps}) inhabiting an anthropogenic landscape in the ghost mining town of Bodie, CA has historically been interpreted as a true metapopulation where dispersal among patches of habitat plays a definitive role in its population dynamics. However, this assumption has never been explicitly demonstrated; in fact, it has been challenged by two competing hypotheses. The first suggests that, rather than patches being roughly equal in size and connectivity as in a metapopulation, large patches act as mainlands, making the landscape a classical MacArthur-Wilson island-mainland system. The second hypothesis suggests that observed occupancy patterns are a result of spatially correlated extinction events; in this hypothesis, dispersal plays a negligible role. Here we show, using 20 years of empirical patch occupancy data, that dispersal must be a key driver of the population dynamics of the Bodie pikas. Furthermore, a Hanski Incidence Function Model, which has become a standard modeling framework for metapopulations, fits the data better than do models of the other two hypotheses. In addition, the metapopulation concept has much more predictive and explanatory power. The Bodie pika population is well-suited to provide insight into fragmented population dynamics because it is distributed over discrete habitat patches, and we possess a series of high-quality censuses of the population from 1972 to 2010. It has become a standard empirical model of the effects of habitat fragmentation; therefore, it is critical that we have an accurate picture of the drivers of its population dynamics.
SMB 2017 Contributed Talk Abstract

A. Authors

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B. Title and Abstract

Anomalous invasion speeds in highly polymorphic populations

Environmental and climate change pose new challenges to the natural world, and many species are adapting to this change by shifting their ranges. Dispersal and population growth rate have been identified as key among the many contributing factors to this complicated process. Previous work has shown that a population with two phenotypes (with the possibility of mutation at birth between them), differing in both their dispersal and reproductive abilities, exhibits “anomalous” invasion speeds – i.e., can invade at a faster rate than a monomorphic population containing either phenotype alone. However in nature there are often a range of dispersal and reproductive abilities within a population. In this talk I will examine the case for a population with a general number of phenotypes. We have used a mathematical modelling approach using a system of generalised Lotka-Volterra partial differential equations and numerical calculations to confirm our findings. The results showed that faster invasion speeds were still possible but were dependent on the parameters of only two particular phenotypes – all other phenotypes did not contribute. Surprisingly, we found that this invasion speed need not be determined by the most dispersive nor the most fecund phenotypes. We found that the conditions for anomalous invasion speeds were dependent on the form of a dispersal-reproduction trade-off. These results have important repercussions for predicting the rate of invasion, and evolution of dispersal during range expansions.
Can trapping invasive crayfish help to save California newts?

We introduce a discrete mathematical model for studying the population dynamics of the California newt (*Taricha torosa*), a species of special concern in California. Predation by invasive crayfish (*Procambarus clarkii*) has decimated newt reproduction and caused local newt extinctions in some Santa Monica Mountain (SMM) streams. We construct a hybrid, stage-structured mathematical model to study whether trapping of invasive crayfish can prolong newt persistence and prevent local newt extinctions. Specifically, we evaluate whether coexistence is possible and determine under what conditions trapping can eliminate the crayfish population. We evaluate which crayfish trapping schedules best protect newt populations. We predict and quantify how crayfish extinction and newt persistence become more likely as the quantity of trapping resources, frequency of trapping implementation, and susceptibility of the crayfish population to trapping increases. We quantify the effectiveness of different crayfish trapping regimes at delaying the time until the newt population goes extinct. Predictions made with our model inform restorative efforts and crayfish management.
1 A. Authors

- Nathan G. Marculis - Department of Mathematical and Statistical Sciences, Centre for Mathematical Biology, University of Alberta, Edmonton, AB T6G 2G1, Canada - marculis@ualberta.ca
- Roger Lui - Department of Mathematical Sciences, Worcester Polytechnic Institute, Worcester, MA 01609, USA - rlui@wpi.edu
- Mark A. Lewis - Department of Mathematical and Statistical Sciences, Centre for Mathematical Biology, University of Alberta, Edmonton, AB T6G 2G1, Canada - mark.lewis@ualberta.ca

Nathan G. Marculis is the presenter.

2 B. Title and Abstract

Title: Neutral Genetic Patterns for Expanding Populations

Abstract: The aim of this work is to investigate the effect that range expansions have on the neutral genetic diversity of a population with nonoverlapping generations. We develop a model by decomposing the population into neutral genetic components and analyze the spatiotemporal evolution of said components. The analysis shows that the concept of pulled fronts are synonymous with the founder effect in population genetics and that overcompensation has no impact on genetic diversity in the expanding population. However, growth functions with a strong Allee effect cause the traveling wave solution to be a pushed front promoting the genetic variation in the population. In this case, the contribution of each neutral fraction can be computed by a simple formula dependent on the initial distribution of the neutral fractions, the traveling wave solution, and the asymptotic spreading speed.
Tipping points in resource abundance drives changes in community structure

Abstract: Global climate change has made what were seemingly extraordinary environmental conditions, such as prolonged droughts, commonplace. Perturbations to limiting resources are likely to be affected by such environmental changes. How will these potentially extreme resource changes impact biodiversity? We developed a trait-based consumer-resource model to examine how changes in resource abundance affects the potential for adaptive evolution and coexistence among competitors. We found that moderate changes in resource abundance have little effect on trait divergence. However, when resource scarcities were sufficiently extreme, a critical transition—a tipping point—occurred, which caused consumer traits to diverge and re-structured the community in a way that outlasted the scarcity. Therefore, even though traits can evolve in response to resource fluctuations in a changing environment, large environmental shifts may be more important in producing long-lasting impacts to community structure. These results may also help to understand patterns of stasis frequently observed in nature, despite the considerable evidence demonstrating rapid evolutionary change.
Authors:
Vadim A. Karatayev, Department of Environmental Science and Policy, University of California, Davis, vkaratayev@ucdavis.edu (presenting author)

Marissa L. Baskett, Department of Environmental Science and Policy, University of California, Davis, mlbaskett@ucdavis.edu

Title:
Spatial scales of alternative stable states in demographically open systems

Abstract:
Although alternative stable states are thought to occur in many ecological systems, their presence in most cases is predicted based on spatially implicit, deterministic models, and the best evidence for this phenomenon remains limited to demographically closed, well-mixed ecosystems such as lakes. By contrast, in many ecosystems thought to exhibit alternative stable states, the synchronizing effect of dispersal among demographically open local communities is counteracted by environmental variation which decouples dynamics across space. Simple spatial models have shown that the relative intensity of these processes determines whether alternative stable states manifest at localized or system-wide scales. However, because the nature and extent of both dispersal and environmental variation differ greatly across systems, the scale at which alternative stable states may occur in most ecosystems is unknown. In kelp forests, the intensity of dispersal and environmental variation are prolifically high and rapid transitions between distinct, temporally persistent forested and urchin barren community states have been repeatedly characterized worldwide. Using a spatially explicit kelp forest community model incorporating forested and barren states, we find that alternative stable states are likely to occur at local rather than system-wide scales under observed levels of environmental variability, despite high dispersal levels in the system. In particular, our model predicts that undesired urchin barren states may manifest over 1-20km of coastline and persist for decades. This spatiotemporal scale is consistent with both empirical observations of kelp forest dynamics and highlights that management efforts to maintain productive forested states may be most effective when focused at local scales. Finally, we point out that despite intense environmental variability, the spatiotemporal dynamics of communities are interactively regulated by both the spatial extent of disturbances and the ecological features of the system.
Authors:

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Title:
“Optimal fishery harvesting modeling the effects of habitat degradation”

Abstract:
Currently, there is considerable overexploitation of our marine fish populations. In addition, the harvesting of fish stock has led to fishing-driven habitat damage and degradation, reducing the habitat’s ability to sustain fish stock populations. These concerns have called for an improved understanding of spatiotemporal dynamics of resource stocks and their respective habitats, as well as their harvesters. In order to optimally solve management strategies that address these issues, we develop a mathematical model for both a fish stock as well as a habitat resource. Both are modeled using nonlinear, parabolic partial differential equations, where the growth rate of the fishery stock is dependent on the habitat. We consider varying movements and boundary conditions. The objective is to find harvest rates that maximize the discounted yield while minimizing the negative effects of harvesting on the habitat. Optimal harvesting strategies are found numerically.
CS15: Computational Biology

Thursday, July 20
3:00–5:00
Officer’s Club East

List of Talks:

- *Modeling the linking of a partial immune response and RSV A2 in human populations*
  Gilberto Gonzalez-Parra*, Hana M. Dobrovolsky

- *Modeling Hepatitis B Virus Entry*
  Tatsuya Kurusu*, Koichi Watashi, Shingo Iwami

- *Design principles of poliovirus defective interfering particles*
  Elsa Rousseau*, Jakub Voznica, Yuta Shiogane Igor Rouzine, Raul Andino, Simone Bianco

- *Insights from a gene network model of cellular aging on lifespan extension effect of dietary restriction*
  Hong Qin*
A. Authors.
   - Gilberto Gonzalez-Parra (Presenter), Department of Physics & Astronomy, Texas Christian University, Fort Worth, TX, USA.
   - Hana M. Dobrovolny, Department of Physics & Astronomy, Texas Christian University, Fort Worth, TX, USA.

B. Title: Modeling the linking of a partial immune response and RSV A2 in human populations.

Abstract: Respiratory syncytial virus (RSV) is a pathogen that can cause serious illness and deaths, particularly in infants, elderly and immunocompromised adults. Here we present several simplified within-host mathematical models that take into account the interaction between the virus and part of the immune system represented by the antibodies IgA. Our aim is to explain from a phenomenological point of view the growth and decay of virus and antibodies in respiratory syncitial virus infections. In order to test the proposed models we use data from a challenge study where both RSV viral titer and IgA have been collected. We estimate the parameters of the models, which allow us to predict and simulate different scenarios regarding viral load and antibodies. In addition, we show that the models, despite the irregularity of the data, describe some essential features of the kinetics of IgA titers against RSV.
Authors
Tatsuya Kurusu¹ (presenter), Koichi Watashi², Shingo Iwami¹,³

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Title
Modeling Hepatitis B Virus Entry

Abstract
Hepatitis B virus (HBV) is one of causative agent for hepatic disease. Although we can prevent new HBV infection with vaccination, we have few specific drug against HBV infection. To develop anti-HBV drugs, the HBV entry step is considered as one of the important targets, and therefore we need to quantitatively understand the step. In this study, we developed a mathematical model describing the HBV entry, analyzed the experimental datasets during the entry step, and estimated the kinetic parameter values for the viral cell-attachment and detachment rate, cell-endocytosed rate, nuclear-entry rate and decreasing rate of covalently closed circular DNA (cccDNA). Based on these estimated parameter values, we simulated the predicted the kinetics of the HBV entry. In addition, stochastic simulations were conducted with hypothetical drugs having different mechanism of action; inhibition on the viral attachment, the viral internalization, and the cccDNA formation, respectively. In our simulations, the percentages of trials in which cccDNA do not appear at 12 days among the total simulated trials were calculated. Interestingly, we found that the inhibition on the viral attachment is the most effective target.
Subject : SMB 2017 Contributed Talk Abstract

A. Authors :
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B. Title and abstract

Design principles of poliovirus defective interfering particles

Defective interfering particles (DIPs) are viral deletion mutants lacking essential elements to complete their viral cycle. They need to be in presence of the wild-type (WT) virus within-cells to complete their cycle and further propagate. By competing for essential elements produced by the WT, they act as molecular parasites of viruses. Thus, engineered DIPs have been proposed as therapies for a number of diseases. Here we will focus on WT poliovirus and associated DIPs lacking genes encoding for capsid proteins. We use a combination of mathematical modeling, numerical simulations and competition experiments to investigate the intracellular and intercellular dynamics of WT and DIPs co-infection in Poliovirus. Our mathematical models are based on Rouzine and Weinberger (Journal of Virology, 2013). At the intercellular level, of special focus here, DIPs and WT spread is described by a Susceptible-Infected based model. Using analytical results and numerical simulations, we provide key elements for the design of DIPs based on capsid stealing that will successfully compete with and displace the WT virus. Competition experiments helped design and validate our theoretical work. Further, we will generalize the developed models to additional viral species.
SMB 2017 Contributed Talk Abstract

Authors: Hong Qin, Department of Computer Science and Engineering, Department of Biology, Geology, and Environmental Science, SimCenter, University of Tennessee at Chattanooga, Chattanooga, TN 37403

Title: Insights from a gene network model of cellular aging on lifespan extension effect of dietary restriction

Abstract:

Biological aging is a complex phenotype with many genes involved, and is characterized by an exponential increase of mortality rate. Dietary restriction is a lifespan extension method that is conserved among many species. We have developed a probabilistic gene network model for cellular aging that can capture the emergent aspect of cellular aging. We applied our network model to study the lifespan extension effect of calorie restriction, including lifespan data sets measured in yeast strains with deletion of SIR2 and TOR1, and in different glucose concentrations. Our results suggest that gene network robustness plays a major role in the effect of dietary restriction. Our results show that network model for aging can offer new insights on molecular mechanism of cellular aging.
Minisymposia

MS1: Mathematics to Support Drug Discovery and Development
Mini-Symposium Title: Mathematics to Support Drug Discovery and Development

Organizer: Richard Allen, Internal Medicine Research Unit, Pfizer Inc, 1 Portland Street, Cambridge, MA, USA

Abstract

A given novel-drug has only about a 10% chance of being approved for treatment. This staggering failure rate reflects the complexity of (patho)-physiology, and the challenges associated with attempting to modulate that complexity safely and efficaciously. A variety of mathematical approaches are being used, in both academia and industry, to address some of these challenges and hopefully bring new therapies to patients faster. This mini-symposium will touch on approaches to four of these challenges:

- Will this drug modulate the disease?
- How can I know if, and how hard, a drug is inhibiting/activating the target?
- When should I dose a drug to maximize efficacy, and minimize side-effects?
- Understanding and predicting the response to a drug in different systems (different cells or organisms).

The scope of this mini-symposium is intentionally quite broad (multiple disease areas, with contributions from industry and academia). This should give those in the audience with no exposure to this area an appreciation of how mathematics is being applied to efficiently identify and develop new therapies. I also believe that practitioners in this area will find the session enlightening via the specific case-studies, and novel approaches presented.
Schedule:

- *Assessing fructose metabolism by analysis of essential fructosuria phenotype*
  Richard Allen*, C. J. Musante, Pfizer Inc.
  10:30 - 11:00

- *A model of neutrophil production to minimize chemotherapy-induced neutropenia*
  Jacques Belair*, M. Craig, A. R. Humphries, M. C. Mackey, F. Nekka, J. Li
  11:00 - 11:30

- *Using models to drive critical decisions from research through clinical trials*
  John M. Burke
  11:30 - 12:30

- *Quantitative translation of drug responses across cell types*
  Jingqi Gong*, Eric A. Sobie
  11:30 - 11:45
Assessing Fructose Metabolism by Analysis of the Essential Fructosuria Phenotype

R.J. Allen*, C.J. Musante,

Internal Medicine Research Unit, Pfizer Inc., 1 Portland Street, Cambridge, MA, USA

Abstract

Fructose is a major component of Western diets and is implicated in the pathogenesis of obesity and type 2 diabetes. In response to an oral challenge, the majority of fructose is cleared during “first-pass” liver metabolism, primarily via phosphorylation by ketohexokinase (KHK). A rare benign genetic deficiency in KHK, called essential fructosuria (EF), leads to altered fructose metabolism. The only reported symptom of EF is the appearance of fructose in the urine following either oral or intravenous fructose administration. Here we develop and use a mathematical model to investigate the adaptations to altered fructose metabolism in people with EF. Firstly, the model is calibrated to fit available data in normal healthy subjects. Then, to mathematically represent EF subjects we systematically implement metabolic adaptations such that model simulations match available data for this phenotype. We hypothesize that these modifications represent the major metabolic adaptations present in these subjects. This modeling approach suggests that several other aspects of fructose metabolism, beyond hepatic KHK deficiency, are altered and contribute to the etiology of this benign condition. Specifically, we predict that fructose absorption into the portal vein is altered, peripheral metabolism is slowed, renal re-absorption of fructose is mostly ablated and that alternate pathways for hepatic metabolism of fructose are up-regulated. Moreover, these findings have implications for drug discovery and development, suggesting that the therapeutic targeting of fructose metabolism could lead to unexpected metabolic adaptations, potentially due to a physiological response to high fructose conditions.
A Model of Neutrophil Production to Minimize Chemotherapy-induced Neutropenia

Jacques Bélair*, 1, M. Craig 2, A.R. Humphries 3, A.R. Humphries 3, M. C. Mackey 3, F. Nekka 1, J. Li 1

1 Université de Montréal, 2 Harvard University, 3 McGill University

We present a physiologically realistic model (stage-structured, transformed into a system of delay-differential equations) to mathematically characterize the neutrophil production in the bone marrow which we then integrate with pharmacokinetic and pharmacodynamic (PKPD) models of a chemotherapeutic agent and an exogenous form of G-CSF (recombinant human G-CSF, or rhG-CSF). Model parameters represent the average values for a general patient and are extracted from the literature or estimated from available data. The dose effect predicted by the model is confirmed through previously published data. Using our model, we were able to determine clinically relevant dosing regimens that advantageously reduce the number of rhG-CSF administrations compared to original studies while significantly improving the neutropenia status. More particularly, we determine that it could be beneficial to delay the first administration of rhG-CSF to day seven post chemotherapy and reduce the number of administrations from ten to three or four for a patient undergoing 14-day periodic chemotherapy.
Using Models to Drive Critical Decisions from Research through Clinical Trials

John M Burke*

Applied BioMath, LLC, Lincoln, MA, United States

Abstract

Quantitative Systems Pharmacology (QSP) is a mathematical modeling and engineering approach to translational medicine that aims to quantitatively integrate knowledge about therapeutics with an understanding of its mechanism of action in the context of human disease mechanisms. The goal of QSP modeling is “to understand, in a precise, predictive manner, how drugs modulate cellular networks in space and time and how they impact human pathophysiology [1].” In doing so, QSP approaches de-risk projects, accelerate the development of best in class therapeutics, and reduce late stage attrition rates. This results is helping industry save money, accelerate timelines, and make better therapeutics, ultimately improving patients’ lives. In the five years since the NIH QSP Working Group met last on this topic, progress has been made to advance this science and to integrate QSP approaches in the drug discovery and development process in industry. Here several case studies will be shown that highlights examples of QSP efforts that have accelerated the discovery and development of best-in-class therapeutics, and impacted critical decisions, in the continuum from preclinical exploration to clinical research. Examples include: providing biological understanding, impacts on new target proposals, lead generation, clinical candidate selection, IND support, and clinical trial go/no go decisions from industry.
Quantitative translation of drug responses across cell types

Jingqi QX Gong*, Eric A. Sobie

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Abstract

The use of human iPSC derived cardiac myocytes (hiPSC-CMs) has changed the landscape of drug development, but the potential of hiPSC-CMs is always limited by its physiological differences from human adult myocytes and quantitative translation of drug effects across cell types remains challenging.

Combining quantitative physiology and statistical analysis approaches, we developed a mathematical modeling based platform that translates drug effects across cell types with quantitative accuracy. Simulations were performed in human adult myocyte and hiPSC-CM dynamical models with heterogeneous cell populations. Regression methods were then used to develop a highly predictive model ($R^2 = 0.93$) that predicts human myocyte action potential and calcium transient features (duration, amplitude, etc) from simulation results in the hiPSC-CM model. Both selective and non-selective ion channel blockers were simulated to test the predictive strength. Predicted drug effects are quantitatively more accurate than hiPSC-CM responses alone. Moreover, in the cases where there is no obvious effect in hiPSC-CMs, our model correctly identified the drug induced changes in human myocytes.

We addressed the question of translating drug effects across different cell types with mathematical approaches and resulted in a potentially practical tool to facilitate drug development.
Mathematical Epidemiology Subgroup
Minisymposium on “Dynamics of Infection”

Organizers

David Earn and Jonathan Dushoff, McMaster University
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Summary

The study of infectious disease transmission dynamics has a long history in mathematical biology, dating back to Daniel Bernoulli in the 18th century. Theoretical developments in modelling the ecology and evolution infectious diseases are important both for practical applications to disease control, and more generally for improving our understanding of ecological interactions and ecosystem dynamics.

In recent years there have been exciting developments in the theoretical foundations of eco-evolutionary dynamics and in the statistical tools used to fit models to data, make predictions and assess performance.

This minisymposium will cover a broad range of topics relevant to dynamics and spread of infectious diseases.

Intended Audience

Attendees interested in dynamics and qualitative analysis, biological applications in general, or infectious disease spread in particular.
Schedule:

- *The population genetics of pathogen virulence*
  Todd Parsons, Troy Day, Sylvain Gandon and Amaury Lambert
  10:30 - 11:00

- *Can reduced predation offset negative effects of parasites on their prey?*
  Mark Lewis, Stephanie Peacock, Brendan Connors, Martin Krkoek and James Irvine
  11:00 - 11:30

- *Identifiability and uncertainty in modeling disease dynamics*
  Marisa Eisenberg
  11:30 - 12:00

- *The Pace of Plague*
  David Earn*, Junling Ma, Ben Bolker, Hendrik Poinar and Jonathan Dushoff
  12:00 - 12:30
Todd Parsons

CNRS and Université Pierre et Marie Curie (Paris 6),
Laboratoire des Probabilités et Modèles Aléatoires,
Paris, France

Joint work with Troy Day, Sylvain Gandon and Amaury Lambert.

“The population genetics of pathogen virulence”

Life history theory provides a powerful framework to understand the evolution of pathogens in both epidemic and endemic situations. This framework, however, relies on the assumption that pathogen populations are very large and that one can neglect the effects of demographic stochasticity. In my talk, I will present an alternative approach, based in population genetics, which will explore the effects of finite population size on the evolution of pathogen virulence and transmission. I will show that demographic stochasticity introduces additional evolutionary forces that can affect qualitatively the dynamics and the evolutionary outcome. In particular, I will discuss scenarios where finite population size can either select for lower or higher virulence.
Mark Lewis

University of Alberta, Department of Mathematical and Statistical Sciences, Edmonton, Alberta, Canada

*Joint work* with Stephanie Peacock, Brendan Connors, Martin Krkošek and James Irvine.

“Can reduced predation offset negative effects of parasites on their prey?”

The impact of parasites on hosts is invariably negative when considered in isolation, but may be complex and unexpected in nature. For example, if parasites make hosts less desirable to predators then gains from reduced predation may offset direct costs of being parasitized. We explore these ideas in the context of parasitic sea louse infestations on salmon. Motivated by data, we use a mathematical model to show how a parasite-induced shift in predation pressure from chum salmon prey to pink salmon prey could offset negative direct impacts of sea lice parasites on chum salmon. This shift in predation is proposed to occur because predators show an innate preference for pink salmon prey that increases when the salmon are parasitized. Our results indicate how the ecological context of host–parasite interactions may dampen, or even reverse, the expected impact of parasites on host populations.
“Identifiability and uncertainty in modeling disease dynamics”

Connecting dynamic models with data often requires a variety of parameter estimation, identifiability, and uncertainty quantification techniques. These approaches can help to determine what is possible to estimate from a given model and data set, and help guide new data collection. Here, we examine how parameter estimation and disease forecasting are affected when examining disease transmission via multiple types or pathways of transmission. Using examples taken from cholera outbreaks in Haiti, Angola, and Thailand, as well as the West Africa Ebola epidemic, we illustrate some of the potential difficulties in estimating the relative contributions of different transmission pathways, and show how alternative data collection may help resolve this unidentifiability. We also illustrate how even in the presence of large uncertainties in the data and model parameters, it may still be possible to successfully forecast the disease dynamics.
David Earn

McMaster University, Department of Mathematics and Statistics,
Hamilton, Ontario, Canada

Joint work with Junling Ma, Ben Bolker, Hendrik Poinar and Jonathan Dushoff.

“The Pace of Plague”

A variety of historical records reveal the temporal patterns of a sequence of plague epidemics in London, England, in the 14th, 16th and 17th centuries. The last plague epidemic in London was the Great Plague of 1665. We use recent methodology to find maximum likelihood estimates and confidence intervals for the initial rates of growth of all the London plague outbreaks for which we have mortality data. We compare the growth rates and consider the implications for the ecology and evolution of Yersinia pestis.
Title: Modeling Blood Flow and Oxygen Transport in the Microcirculation

Organizers: Brendan Fry, Metropolitan State University of Denver, bfry2@msudenver.edu  
Philip Pearce, Massachusetts Institute of Technology, ppearce@mit.edu

Summary:
The microcirculation is the part of the circulation consisting of the smallest blood vessels in the body, and is the location of the majority of oxygen exchange between vessels and surrounding tissue. Deficiencies in oxygen delivery have been implicated in various diseases, as the proper matching of oxygen supply and demand is essential to preserve tissue viability. At the microvascular level, complex networks of vessels make experimental approaches to studying blood flow and oxygen transport insufficient to determine all the mechanisms present to ensure matching of oxygen supply and demand; as such, mathematical modeling approaches are a necessary supplement, allowing researchers to simulate processes that cannot be individually modulated in a lab.

This minisymposium will bring together researchers using mathematical modeling to address problems involving blood flow and oxygen transport in the microvasculature of various tissues, including the skeletal muscle, brain, eye, kidney, and placenta. The goal will be to expose the different modeling techniques used to describe flow and transport in these different vascular beds, and determine if there are techniques being used with one type of tissue that could be used for others. Such overlapping modeling strategies will promote collaboration, and help advance research into the mechanisms underlying oxygen delivery in the microvasculature of a variety of tissues. The minisymposium is intended for those studying the microcirculation, in specific organs or at a fundamental level, at any stage in their research careers. The talks will also be useful for any researcher who would like a broad introduction to the research being done on oxygen transport, blood flow, and the microcirculation.
MS3

Modeling Blood Flow and Oxygen Transport in the Microcirculation

Monday, July 17, 10:30–12:30, Officer’s Club North

Schedule:

- *Modeling microvascular blood flow and oxygen transport in tissues with non-uniform structure*
  Brendan Fry
  10:30 - 10:50

- *Models for blood flow and oxygen transport in the brain*
  Timothy Secomb*
  10:50 - 11:15

- *Elucidating the role of blood flow in glaucoma using a Green’s function method*
  Julia Arciero*
  11:15 - 11:40

- *Hemodynamics and Blood-Tissue Oxygen Transport in Complete Arteriolar-Venular Networks of the Rat Gluteus Maximus Muscle*
  Daniel Goldman*, Zahra Farid, Kent A. Lemaster, Jefferson C. Frisbee, Dwayne N. Jackson
  11:40 - 12:05

- *Blood flow and oxygen transfer in feto-placental capillary networks*
  Philip Pearce*
  12:05 - 12:30
Author: Brendan Fry*, Metropolitan State University of Denver, bfry2@msudenver.edu

Title: Modeling microvascular blood flow and oxygen transport in tissues with non-uniform structure

Abstract:
Research in mathematical modeling of the microcirculation has been directed towards building models that capture the detailed dynamics of blood flow either directly or via simplified means. An enhanced understanding of the local and global properties of blood flow, and simplified methods for taking them into account in models, has enabled recent simulations of flow and oxygen transfer in microvascular networks obtained using experimental data. Networks such as these, often specific to particular organs, present their own challenges, and it is important that researchers studying different organs communicate to share ideas and keep abreast of developments in fundamental microcirculatory research – a main goal of this minisymposium.

Here, an overview of the microcirculation and the non-uniform structure of microvascular networks will be provided, to demonstrate the need for mathematical modeling approaches as a necessary supplement in microvascular research. Then, a specific theoretical model will be presented to analyze the impact on oxygen distribution of the heterogeneous organization of the inner part of the rat kidney – called the medulla – revealed in anatomical studies. This “region-based” model represents the 3D architecture of the renal medulla and the resulting preferential interactions among tubules and vessels by specifying the radial positions of those tubules and vessels within interconnected regions. Results of the model suggest that the structural organization of the renal medulla produces marked axial and radial tissue oxygen concentration gradients. In addition, the heterogeneous structure preserves oxygen delivery deep into the kidney, but significantly increases the likelihood of oxygen-limiting tissue injury.
Author: Timothy Secomb*, University of Arizona, secomb@u.arizona.edu

Title: Models for blood flow and oxygen transport in the brain

Abstract:
Brain function is critically dependent on adequate oxygen supply. In humans, the brain accounts for about 2% of body mass and about 20% of resting oxygen consumption. When deprived of oxygen, brain neurons suffer irreversible damage in about 5 minutes. The maximum distance that oxygen can diffuse into cortical tissue is typically about 60 µm. Therefore, brain oxygenation is sensitive to the spatial arrangement and the blood flow rates of the microvessels. We have developed a Green’s function method that allows efficient computation of the oxygen fields surrounding microvessel networks with experimentally determined three-dimensional structures and flow rates. The resulting distribution of partial pressure of oxygen in tissue is substantially wider than predicted by a corresponding Krogh cylinder model. The occurrence of hypoxia is particularly sensitive to oxygen consumption rate, such that the hypoxia resulting from a severe (75%) reduction in perfusion can be avoided by a moderate (31%) decrease in oxygen consumption rate. Blood flow rate in the cortex increases locally in response to neural activation (neurovascular coupling), causing the oxyhemoglobin saturation to increase. This phenomenon forms the basis for functional magnetic resonance imaging, but its physiological mechanisms are not well understood. Surprisingly, the increase in blood flow with activation is not dependent on local oxygen levels. Thus, the maintenance of adequate oxygen levels appears to depend instead on structural adaptation of microvascular networks. Simulations of oxygen transport in brain tissue are a key component of studies aimed at understanding these important physiological phenomena. Supported by NIH grants HL034555 and HL070657.
Title: Hemodynamics and Blood-Tissue Oxygen Transport in Complete Arteriolar-Venular Networks of the Rat Gluteus Maximus Muscle

Abstract:

The importance of network properties of the microvasculature has been recognized for several decades. However, detailed investigation of the effects of network structure on blood flow, blood-tissue exchange and flow regulation has received less experimental emphasis as of late. Therefore, our research group has been using intravital videomicroscopy (IVVM) to determine complete arteriolar and venular network structure in a rat gluteus maximus (GM) muscle preparation that we recently developed. We have also been working to determine how the arteriolar and venular networks supply and drain (respectively) capillary beds, and how the integrated arteriolar/capillary/venular network determines and regulates blood flow. Since the purpose of tissue blood flow is mainly the delivery of oxygen to parenchymal cells (in this case myocytes), we have begun using a computational model to investigate oxygen transport between our microvascular networks and the surrounding tissue. This work uses a discrete description of arterioles and venules coupled to a tissue model containing continuously distributed capillaries. For baseline blood flow and oxygen consumption, we present results showing the loss of oxygen from arterioles, the tissue oxygen distribution, and the uptake of oxygen by venules. We then present results for both global and local increases in oxygen consumption, with and without oxygen-dependent flow regulation. These simulation results will be tested against experimental data, with the ultimate goal of building a detailed, validated model of transport and flow regulation in the rat GM muscle.
Author: Philip Pearce*, Massachusetts Institute of Technology, ppearce@mit.edu

Title: Blood flow and oxygen transfer in feto-placental capillary networks

Abstract:
During pregnancy, oxygen diffuses from maternal to fetal blood through placental tissue. A multi-scale model of the human placenta will require the simulation of blood flow and oxygen transfer in large feto-placental capillary networks. In this work, a model is described which allows such simulations to be performed. Realistic hemodynamic effects such as plasma skimming are taken into account and oxygen transfer is calculated by treating capillaries as modified Krogh cylinders. Two main uses of the model are illustrated. First, the effect of network structure and hematocrit on fetal oxygen supply are investigated. Second, simulations are performed on realistic geometries, generating results to be coupled to simulations of flow and oxygen transfer in larger vessels in future multi-scale simulations.
MS4: Neuromechanical Motion

SMB 2017 Minisymposium

Title: Neuromechanical Locomotion

Organizer: Kathleen Hoffman, 1000 Hilltop Circle, UMBC, Baltimore, MD 21250, khoffman@umbc.edu

Summary:
Locomotion, whether it’s flying, walking or swimming, involves complex interactions between the nervous systems, muscles, and environmental forces. While there are systems, such as muscle, that are common among species and locomotion-type, there are also features of locomotion that are specific to the type of locomotion and species. For example, heel strike is an important aspect of walking, whereas fluid forces play an important role in swimming and flying. Speakers in this minisymposium will give an overview ongoing research and current questions in neuromechanical locomotion across a broad range of species and types of locomotion.
Schedule:

- **An Introduction to Neuromechanical Locomotion**
  Kathleen Hoffman
  10:30 - 10:45

- **System identification of components of locomotor systems and their effects on closed-loop behavior**
  Tim Kiemel
  10:45 - 11:10

- **Gait transitions in a phase oscillator model of an insect central pattern generator**
  Zahra Aminzare*, Vaibhav Srivastava, Philip Holmes
  11:10 - 11:35

- **Computational modeling of a swimming lamprey and the effects of sensory feedback**
  Christina Hamlet*, Lisa J. Fauci, Kathleen A. Hoffman
  11:35 - 12:00
Title: An Introduction to Neuromechanical Locomotion

Author: Kathleen Hoffman, UMBC, khoffman@umbc.edu

Abstract: Neuromechanical locomotion involves a complex series of interactions between the central nervous system, muscle, body and environment. Sensory organs modulate the locomotor pattern in response to sensory information. I will describe this neuromechanical feedback loop as an introduction to the field of neuromechanical locomotion.
Title: System identification of components of locomotor systems and their effects on closed-loop behavior

Author: Tim Kiemel, University of Maryland, kiemel@umd.edu

Abstract: Locomotion results from closed-loop interactions among the nervous system, the rest of the body, and the environment. Activation of muscles by the nervous system causes movement (the plant in control theory). However, movement also causes muscle activation (neural feedback). Movement is sensed by visual, somatosensory and vestibular systems, and the nervous system activates muscles based on this sensory information. For the intact closed-loop behavior of human walking, we describe an approach to identifying the properties of the plant and neural feedback by measuring responses of muscle activation (measured using electromyography) and movement to continuous sensory and mechanical perturbations. For the lamprey, open-loop experiments can be conducted on neural components of the locomotor system, such as the central pattern generator in the spinal cord. In this case, we describe how to perform open-loop experiments with perturbations to provide characterizations of the system's components that predict closed-loop behavior.
Title: Gait transitions in a phase oscillator model of an insect central pattern generator

Authors:
1. Zahra Aminzare*, Princeton University, aminzare@math.princeton.edu
2. Vaibhav Srivastava, Michigan State University, vaibhav@egr.msu.edu
3. Philip Holmes, Princeton University, pholmes@math.princeton.edu

Abstract:
Legged locomotion involves various gaits. It has been observed that fast running insects (cockroaches) employ a tripod gait with three legs lifted off the ground simultaneously in swing, while slow walking insects (stick insects) use a tetrapod gait with two legs lifted off the ground simultaneously. Fruit flies use both gaits and exhibit a transition from tetrapod to tripod at intermediate speeds. In this work, we study the effect of stepping frequency on gait transition in an ion-channel bursting neuron model in which each cell represents a hemi-segmental thoracic circuit of the central pattern generator. Employing phase reduction, we reduce the network of bursting neurons represented by 24 ordinary differential equations to 6 coupled nonlinear phase oscillators, each corresponding to a network controlling one leg. Assuming that the left legs maintain constant phase differences with the right legs (contralateral symmetry), we reduce from 6 equations to 3, allowing analysis of a dynamical system with 2 phase differences defined on a torus. We show that bifurcations occur from multiple stable tetrapod gaits to a unique stable tripod gait as speed increases. Finally, we consider gait transitions in two sets of data fitted to freely walking fruit flies.
Title: Computational modeling of a swimming lamprey and the effects of sensory feedback

Authors:
*Christina Hamlet, Bucknell University, USA, ch051@bucknell.edu
Lisa J. Fauci, Tulane University, USA, fauci@tulane.edu
Kathleen A. Hoffman, University of Maryland, Baltimore County, USA, khoffman@umbc.edu
Eric Tytell, Tufts University, USA, eric.tytell@tufts.edu

Abstract:

The lamprey is a model organism for both neurophysiology and locomotion studies. Studying a flexible body coupled to its fluid environment sheds light into swimming performance and efficiency. Animals use proprioceptive (body-sensing) information to detect how their bodies are bending, and then adjust the neural signals to their muscles to improve performance. Here we present a computational swimming lamprey driven by a central pattern generator (CPG) modeled as a chain of coupled oscillators. The CPG drives muscle kinematics in fluid-structure interactions implemented in an immersed boundary framework to produce the emergent swimming mode. Different functional forms of body curvature changes provide sensory feedback to the CPG. Comparison of these functional forms and how these may be used to investigate feedback in natural lamprey are presented. Effects of feedback to the neural activation on swimming performance are estimated and examined.
Title: The control of insect flight: a confound of sensory feedback in nature and the laboratory

Author: Eatai Roth Department of Biology, University of Washington, Seattle, WA 98195 eatai@uw.edu

Abstract: As animals navigate through and interact with their environment, they rely on cues pooled across multiple sensory systems to control their movement. Each sensory system provides feedback encoding motion information, both efferent (exogenous motion) and afferent (self-motion); the suite of sensory systems create numerous parallel feedback loops. In the laboratory, we often aim to isolate the behavioral contributions of individual sensory pathways, how stimuli to a particular sensory modality are processed to shape the motion output. But to what extent can we understand the dynamics of a single sensorimotor pathway outside of the context of the multisensory ensemble? As a motivating example, I consider a flower-following behavior in the hawkmoth, Manduca sexta. These moths feed while hovering, drinking nectar from the flower by means of a long proboscis while actively station-keeping; as the flower sways, the moth follows. Leveraging a frequency-domain system identification analysis, Roth et al. (2016) demonstrated that this behavior is mediated by parallel visual and mechanosensory (via the proboscis) pathways and that the dynamic contributions of these modalities sum linearly in the motion output. This control architecture—parallel pathways with linear summation—is perhaps the simplest scheme for sensory integration. Yet, despite the simplicity, in the context of closed-loop behavior this multisensory control system furnishes robustness by means of redundancy. Robustness and redundancy, while a boon to behavior in nature, may confound our attempts to identify sensorimotor dynamics in the laboratory. The choice of experimental paradigm affects the feedback topology of the biological system by selectively opening or closing feedback loops. I compare several experimental approaches—sensory degradation, inhibition, and conflict—to demonstrate how the choice of paradigm affects the interpretation of behavioral data and our ability to isolate and model sensorimotor dynamics. I advocate that sensory conflict is a unique and invaluable tool for identifying the contributions of sensorimotor pathways in multisensory behaviors.
MS5: Recent advances in the analysis of biochemical reaction systems

Minisymposium Title:
Recent advances in the analysis of biochemical reaction systems

Organizers:
Matthew D. Johnston (matthew.johnston@sjsu.edu)
Badal Joshi (bjoshi@csusm.edu)

Summary:
Dynamical models arising from the study of biochemical reaction networks are typically very difficult to analyze by traditional numerical and bifurcation approaches due to their high dimensionality, parameter uncertainty, and varied time-scales. In recent years, the focus has shifted to network-based analysis of these systems with significant contributions from the areas of algebraic geometry, optimization, and stochastic analysis. In this session, we will investigate recent advances with a focus on the following: (i) multistationarity/multistability; (ii) model reduction; and (iii) stochastic/discrete systems.
Schedule:

- *Extensions of absolute robustness to stochastic chemical reaction networks*
  German Enciso
  10:30 - 11:00

- *Inheritance of bistability in mass action reaction networks*
  Casian Pantea
  11:00 - 11:30

- *An Invitation to Pharmacostatics*
  Gilles Gnacadja
  11:30 - 12:00

- *Robust permanence of polynomial dynamical systems*
  James Brunner
  12:00 - 12:30
Extensions of absolute robustness to stochastic chemical reaction networks

Absolute concentration robustness is a property that allows signaling networks to sustain a consistent output in the face of protein concentration variability from cell to cell. This property is structural and can be determined from the topology of the network alone. In this talk, I discuss this concept first for deterministic systems, and then set out to describe their stochastic behavior. In the long term, the corresponding stochastic processes undergo an extinction event that eliminates the robustness. However, these systems have a transiently robust behavior that may be sufficient to carry out the necessary signal transduction in cells.
Inheritance of bistability in mass action reaction networks

We focus on the question of bistability, or existence of multiple stable positive equilibria, a dynamical property that underlies important cellular processes, and a recurring theme in recent work on reaction networks. Namely, we consider the question: “when can we conclude that a network admits multiple stable positive equilibria based on analysis of its subnetworks?” We identify a number of operations on reaction networks that preserve bistability as we build up the network, and we illustrate the power of this approach on the much-studied Huang-Ferrell MAPK cascade. Work in this directions falls broadly under the theory of “motifs”, a central theme in systems biology.
An Invitation to Pharmacostatics

Pharmacology, the study of interactions between biological processes and therapeutic agents, is traditionally presented as consisting of two subdisciplines: pharmacokinetics, which is about the distribution and metabolism of drugs in organisms; and pharmacodynamics, which is about the organisms response to drugs. In discovery-stage pharmacology however, one primary concern is what we call pharmacostatics, the characterization of equilibrium parameters and states of core interactions of physiologic and therapeutic interest. This usually takes the form of studying dose-response curves, without consideration for the relevant qualitative properties of the underlying reaction networks, e.g. the existence, multiplicity and stability of steady states. Furthermore, steady state calculations usually employ manually derived formulas based on approximating assumptions. While these formulas may seem adequate most of the time, the assumptions need not apply, and there are rare but genuine cases where this approach fails to explain non-monotone dose-response curves. We will discuss results and prospects surrounding these issues.
Robust permanence of polynomial dynamical systems

Authors

• James Brunner*, Department of Mathematics, University of Wisconsin - Madison, jdbrunner@math.wisc.edu

• Gheorghe Craciun, Department of Mathematics and Department of Biomolecular Chemistry, University of Wisconsin - Madison, craciun@math.wisc.edu

Abstract

A “permanent” dynamical system is one whose positive solutions stay bounded away from zero and infinity. The permanence property has important applications in biochemistry, cell biology, and ecology. Inspired by reaction network theory, we define a class of polynomial dynamical systems called \( \mathcal{N}\)-tropically endotactic, using a given polyhedral fan \( \mathcal{N} \). We show that these polynomial dynamical systems are permanent, irrespective to the values of (possibly time-dependent) parameters in these systems. These results generalize the permanence of 2D reversible and weakly reversible mass-action systems.
Oncolytic virus therapy (OVT) is the use of a virus to treat cancer. Viruses have been found and engineered to specifically target and kill tumor cells by 1) direct lysis and 2) influence of the immune system. Not only is OVT being applied to solid tumors, but OVT is also being investigated for “liquid” tumors (blood cancers) due to its safety, selectivity, and potency. The mathematical modeling of OVT is keeping in step with current research by applying agent-based modeling, ODEs and PDEs, and multi-scale techniques to describe experimental data in context of the tumor microenvironment. These modeling approaches are employed to capture important facets of geometric and immunological significance. Consequently, math models help predict dosing and sequencing schedules, especially in combination therapies such as chemotherapy, radiation therapy, or immunotherapy. Here we discuss recent models and future directions of OVT modeling.
Schedule:

- *Mathematical models of oncolytic virus therapy*
  Dominik Wodarz
  10:30 - 11:00

- *Oncolytic viral therapies and the interactions with the macrophages*
  Raluca Eftimie
  11:00 - 11:30

- *Treatment Strategies for Combining Oncolytic Virotherapy with Immunostimulation*
  Joanna R. Wares
  11:30 - 12:00

- *Oncolytic virotherapy for the invasive/non-invasive glioma and Bortezomib-induced synergetic effect on tumor killing*
  Yangjin Kim
  12:00 - 12:30
2017 SMB meeting, U of Utah  
Special session: Modeling Viruses to Defeat Cancer (organizer: Dr. Daniel N. Santiago)

Speaker: Dr. Dominik Wodarz (University of California, Irvine; email: dwodarz@uci.edu)

Title: Mathematical models of oncolytic virus therapy

Abstract: Oncolytic viruses infect and kill cancer cells and have the potential to spread throughout tumors. Promising results have been observed in the clinic, although the correlates of successful therapy are not fully understood. Mathematical models can help understand how the multifactorial interactions between viruses and the tumor cells can influence the outcome of oncolytic virus therapy, and these approaches will be reviewed. Particular emphasis will be placed on spatial models of oncolytic virus infections, demonstrating that the dynamics can be rather complex even in simple experimental systems. Implications for clinical development will be discussed.
Speaker: Dr. Raluca Eftimie (University of Dundee; email: r.a.eftimie@dundee.ac.uk)

Title: Oncolytic viral therapies and the interaction with the macrophages

Abstract: Over the past years, oncolytic viruses have generated much interest in cancer therapy, mainly due to the fact that once a virus is injected into the patient it can actively search for cancer cells and destroy them, without significant side effects. However, the anti-tumour effect of oncolytic viruses is greatly diminished by the anti-viral immune response. One of the key players of cancer immunotherapy is represented by the macrophages. However, the role of macrophages in oncolytic virus therapies is underestimated and sometimes controversial. Here, we introduce a mathematical model for cancer-immune-virus interactions, and use it to investigate the delicate balance between the anti-viral and anti-tumour immune responses exhibited by the macrophages.
Authors: Dr. Joanna R. Wares*, University of Richmond, jware@richmond.edu; Dr. Jana L. Gevertz, The College of New Jersey, gevertz@tcnj.edu; Dr. Peter S. Kim, The University of Sydney, pkim@maths.usyd.edu.au

Title: Treatment Strategies for Combining Oncolytic Virotherapy with Immunostimulation

Abstract: Traditionally, oncolytic viruses (OVs) were deemed effective due to their ability to treat cancer by selectively replicating inside of and lysing tumor cells while leaving healthy cells unharmed. However, the efficacy of this process appears limited. To combat these limitations, engineers are designing new OVs that not only replicate quickly inside of cells but that also mediate the release of cytokines and co-stimulatory molecules to attract cytotoxic T cells that then target tumor cells, thus increasing the tumor-killing effects of OVs. Combing immunostimulating OVs with dendritic cell (DC) injections can further improve treatment. To investigate how to best structure this combination treatment, we built a model consisting of a system of ordinary differential equations and fit the model to a rich data set (Huang et al.). We then simulated varying doses of OV and DC injections to test a multitude of treatment strategies and to determine which strategy works best. In this talk, I will describe the model and report our results.
2017 SMB meeting, U of Utah  
Special session: Modeling Viruses to Defeat Cancer (organizer: Dr. Daniel N. Santiago) 

Speaker: Dr. Yangjin Kim (Konkuk University, email: ahyouhappy@gmail.com) 

Title: OV therapy for the invasive/non-invasive glioma and Bortezomib-induced synergetic effect on tumor killing. 

Abstract: In this talk, a mathematical model of Chase-ABC mediated oncolytic virus therapy targeting cancer stem cells and CSPG-driven glioma infiltration will be presented. Glioblastoma is the most aggressive type of brain cancer with the median survival time of one year. Oncolytic viruses are genetically engineered viruses that are designed to kill cancer cells while doing minimal damage to normal healthy tissue. After being injected into a tumor, they infect cancer cells, multiply inside them, and when a cancer cell is killed they move on to spread and infect other cancer cells. Chondroitinase ABC (Chase-ABC) is a bacterial enzyme that can remove a major glioma ECM component, chondroitin sulfate glycosoamino glycans (CSGG) from proteoglycans without any deleterious effects in vivo. It has been shown that Chase-ABC treatment is able to promote the spread of the viruses, increasing the efficacy of the viral treatment. We develop a mathematical model to investigate the effect of the Chase-ABC on the treatment of glioma by oncolytic viruses (OV). We show that the model’s predictions agree with experimental results for a spherical glioma. We then use the model to test various treatment options for both primary tumor and infiltrating tumor cells in the heterogeneous microenvironment of the brain. A new strategy of targeting cancer stem cells in a niche using transported oncolytic viruses will be also presented. The primary treatment option is surgery but invasive cells in brain tissue eventually regrow back even with chemo- and radio-therapy, generating poor clinical outcomes. Therefore, it is important to distinguish invasive glioma phenotypes from non-invasive cells. Experiments by Silver et al illustrated that concentrations of CSPG, one of major extracellular matrix component within a tumor, determine invasive and non-invasive phenotypes. We developed a mathematical model of CSPG-driven dynamics of a growing glioma, using a free boundary framework. We take into account the rich dynamics of astrocytes and microglia in brain tissue as illustrated in Silver et al. The simulation results are in good agreement with experimental data in Silver et al. We also show how oncolytic virus therapy can be used to eradicate tumor cells. There is a critical threshold value of CSPG levels for optimal killing of both invasive and noninvasive tumor cells. We will also present a recent progress in understanding of Bortezomib-OV therapy efficacy and how NK cells can play a role in regulation of OV therapy. We show that bortezomib and OV therapy can have synergetic effects on tumor killing and suggest several hypotheses on the role of NK cells in regulation of mysterious boost of OV therapy efficacy in the absence of NK cells.
MS7: Mathematical and numerical methods for the study of viral hepatitis

SMB 2017: 'Mathematical and numerical methods for the study of viral hepatitis' Mini-symposium
Organizer: Stanca M Ciupe, stanca@vt.edu
Co-organizer: Harel Dahari, hdahari@luc.edu
Title: Mathematical and numerical methods for the study of viral hepatitis

Summary: Approximately 500 million people are living with chronic viral hepatitis worldwide; 1 million of those who are infected die each year, primarily from cirrhosis or liver cancer resulting from their hepatitis B, hepatitis D, and/or hepatitis C infections. While direct-acting antivirals (DAAs) have been recently approved for hepatitis C, barriers to treating people persists and need to be addressed. Commonly used hepatitis B therapies suppress viral replication, but often require lifelong administration to prevent viral rebound. To predict, evaluate, and anticipate the strategies behind universal control of the disease, we bring together experts in modeling viral kinetics who will evaluate and rationalize the effectiveness and shortcomings of antiviral treatment.

Current directions: This mini-symposium brings together modelers and mathematicians who are experts in the study of virus hepatitis diseases. They will show how mathematical techniques can provide insight into the virological and immunological mechanisms governing viral decay after the start of therapy in hepatitis B infection in humans; predict the optimal dose and the timing of drug administration which can best control hepatitis B in humans while minimizing side-effects; investigate the connection between the size of a challenge inoculum and hepatitis B virus dynamics in humanized mice; and present the mathematical challenges behind developing and numerically solving the muti-scale model of molecular mechanisms that was needed to explain the dynamics of the recently discovered and highly potent anti-hepatitis C drugs.

Scope: The goal of the mini-symposium is to discuss current challenges in the field, including the role of mathematics in understanding the basic virological and immunological mechanisms of these infections, the role modeling can play in improving treatment outcomes, and how these findings can be applied to other viral infections.

Intended Audience: This mini-symposium is targeted to both young and established mathematical modelers and clinical researchers interested in modeling virus dynamics, immune responses, and drug therapy in general and in the context of viral hepatitis.
Schedule:

- **Complex Hepatitis B virus profiles during antiviral therapy mathematical and numerical investigation**  
  Andrea Carracedo Rodriguez, Matthias Chung, Stanca M. Ciupe*  
  3:00 - 3:25

- **An agent-based modeling of hepatitis B virus kinetics in humanized chimeric mice**  
  Atesmachew Hailegiorgis*, Yuji Ishida, Michio Imamura, Nobuhiko Hiraga, Hiroshi Yokomichi, Chise Tateno, Susan L. Uprichard, Kazuaki Chayama, Harel Dahari  
  3:25 - 3:50

- **Mathematical modeling of hepatitis C virus (HCV) kinetics during antihistamine chlorcyclizine HC l based treatment**  
  Preeti Dubey*, Christopher Koh, Shanshan He, Michio Imamura, Juan J. Marugan, Kazuaki Chayama, T. Jake Liang, Harel Dahari  
  3:50 - 4:15

- **Optimal control of drug therapy in a hepatitis B model**  
  Jonathan E. Forde*, Stanca M. Ciupe, Ariel Cintron-Arias, Suzanne Lenhart  
  CiupeForde.pdf  
  4:15 - 4:40

- **An efficient and reliable method for the numerical solution of PDE multiscale model with age of hepatitis C virus dynamics**  
  Vladimir Reinharz*, Harel Dahari, Danny Barash  
  4:40 - 5:05
Understanding the complex patterns observed during hepatitis B Virus therapy

Andrea Carracedo Rodriguez 1, Matthias Chung 1, Stanca M Ciupe 1*

1. Department of Mathematics, Virginia Tech, 460 McBryde Hall, Blacksburg, VA, 24060

*Presenter stanca@vt.edu

Data from human clinical trials have shown that hepatitis B virus follows complex profiles such as bi-phasic, tri-phasic, stepwise decay and rebound. We utilized a deterministic model of hepatitis B virus kinetics following antiviral therapy to uncover the mechanistic interactions behind the hepatitis B virus dynamics. Analytical investigation of the model was used to separate the parameter space describing virus decay and rebound. Monte Carlo sampling of the parameter space was used to determine the virological, pharmacological and immunological factors that separate the bi-phasic and tri-phasic virus profiles. We found that the level of liver infection at the start of therapy best separates the decay patterns. Moreover, drug efficacy, ratio between division of uninfected and infected cells, and the strength of cytotoxic immune response are important in assessing the amount of liver damage experienced over time and in quantifying the duration of therapy leading to virus resolution in each of the observed profiles.
An agent-based modeling of hepatitis B virus kinetics in humanized chimeric mice

Atesmachew Hailegiorgis1*, Yuji Ishida2,3, Michio Imamura3, Nobuhiko Hiraga3, Hiroshi Yokomichi2, Chise Tateno2,3, Susan L. Uprichard1, Kazuaki Chayama3,4, Harel Dahari1

(1*) The Program for Experimental & Theoretical Modeling, Division of Hepatology, Department of Medicine, Loyola University Medical Center, Maywood, IL, USA ahailegiorgis@luc.edu; (2) PhoenixBio Co., Ltd., Hiroshima, Japan; (3) Liver Research Project Center, and (4) Department of Gastroenterology and Metabolism, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan;

*presenting author

Hepatitis B virus (HBV) infection imposes an enormous global health burden. As such, there is an urgent need to elucidate the dynamics of HBV-host infection and ultimately treatment response. The uPA/SCID humanized chimeric mouse model is a useful tool for studying the dynamics of HBV infection and treatment response. Interestingly, we found that HBV infection in these mice is highly dynamic (i.e., 7 distinct kinetic phases) despite the absence of an adaptive immune response. Current deterministic differential equation models of HBV infection were not designed to reproduce this highly dynamic picture. To explain these complex kinetics, we have developed a stochastic agent-based model (ABM) in MASON. In the model, human hepatocytes (cells) are defined as the main agents and free virus in blood as a single global agent. Cells are characterized by their infection status and viral production stage. Uninfected cells exposed to HBV become infected but not productive (eclipse phase) until they proceed to the production phase, i.e. able to release virions. Initial model conditions and several model parameters are defined based on experimental design and kinetic analysis. The model reproduces well all 7 distinct serum HBV kinetic patterns observed in chimeric mice. Modeling results predict multiple cycles of infection, a 10-48h eclipse phase and an initial slow, but increasing rate of virus production from each cell play major role in generating the multiphasic HBV kinetic patterns. Further verification and validation of the model are necessary to ensure the robustness of the emerging patterns.
Mathematical and numerical methods for the study of viral hepatitis

Mathematical modeling of hepatitis C virus (HCV) kinetics during antihistamine chlorcyclizine HCl based treatment

Preeti Dubey1*, Christopher Koh2, Shanshan He2, Michio Imamura3, Juan J. Marugan4, Kazuaki Chayama3, T. Jake Liang2, Harel Dahari1

The Program for Experimental & Theoretical Modeling, Division of Hepatology, Loyola University Medical Center, Maywood, Illinois, USA1 pdubey1@luc.edu *; Translational Hepatology Unit, Liver Diseases Branch, National Institute of Diabetes & Digestive & Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA2, Department of Medicine and Molecular Sciences, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan3, National Center for Advancing Translational Sciences, National Institutes of Health, Rockville, MD, USA4

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We recently identified that the antihistamine chlorcyclizine HCl (CCZ) has anti-HCV activity in vitro and in vivo, however CCZ specific mode of action (MOA) is not known. In this study, we sought to provide insights into CCZ MOA against HCV via mathematical modeling of HCV RNA kinetics obtained from patients and uPA/SCID chimeric mice with humanized livers during CCZ-based treatment. In my talk I will present our (i) kinetic characterization of the measured HCV RNA in blood during CCZ ± ribavirin treatments in patients and chimeric mice, (ii) modeling efforts to revealing CCZ MOA in the chimeric mouse model with humanized livers (in the absence of the adaptive immune response), and (iii) modeling efforts to understanding CCZ MOA in patients.
Optimal control of drug therapy in a hepatitis B model

Jonathan E. Forde1*, Stanca M. Ciupe 2, Ariel Cintron-Arias 3, Suzanne Lenhart 4

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Combination antiviral drug therapy improves the survival rates of patients chronically infected with hepatitis B virus by controlling viral replication and enhancing immune responses. Some of these drugs have side effects that make them unsuitable for long-term administration. To address the trade-off between positive and negative effects of the combination therapy, we investigated an optimal control problem for a delay differential equation model of immune responses to hepatitis virus B infection. Our optimal control problem investigates the interplay between virological and immunomodulatory effects of therapy, the control of viremia, and the administration of minimal dosage over a short period of time. Our numerical results show that the \textit{high} drug levels that induce immune modulation rather than suppression of virological factors are essential for clearance of hepatitis B virus.
An Efficient and Reliable Method for the Numerical Solution of PDE Multiscale Model with Age of Hepatitis C Virus Dynamics during Drug Treatment

Vladimir Reinharz¹*, Harel Dahari², Danny Barash¹

¹Department of Computer Science, Ben Gurion University, Israel; ²The Program for Experimental & Theoretical Modeling, Division of Hepatology, Loyola University Medical Center, Maywood, IL, USA. vreinharz@gmail.com *presenter.

Age-structured PDE multiscale models have been developed to study viral dynamics. However, they are notoriously difficult to solve. Here, we investigate the numerical solutions of a PDE multiscale model of hepatitis C virus (HCV) dynamics during antiviral treatment and compare them with the proposed analytical approximation (Proc Natl Acad Sci USA. 2013; 110(10):3991-6). First, starting from a simple yet flexible numerical solution, the Euler method, that also considers an integral approximated over previous iterations, we show that the analytical approximation is an underestimate of the PDE model solution as expected since new infection events are being ignored from initiation of antiviral treatment. We then highlight the importance of having a numerical solution that takes into account previous iterations for the associated integral, impeding the use of canned solvers. Second, we demonstrate that the governing differential equations are stiff and the stability of the numerical scheme should be considered. Third, we show that considerable gain in efficiency can be achieved by using adaptive stepsize methods over fixed stepsize methods for simulating realistic scenarios when solving multiscale models numerically. Finally, we compare between several numerical schemes and show the benefit of using the Rosenbrock method, an implicit adaptive stepsize method that is both efficient and stable.
MS8: Modeling Tumor-Immune Dynamics, Disease Progression, and Treatment

2017 SMB Annual Meeting – Salk Lake City, Utah.

Session Title: Modeling Tumor-Immune Dynamics, Disease Progression, and Treatment

Organizers:
Lisette de Pillis (Mathematics, Harvey Mudd College, Claremont, CA, USA),
depillis@g.hmc.edu
Amina Eladdadi (Mathematics, The College of Saint Rose, Albany NY, USA),
eladdada@strose.edu

The Scope of the mini-symposium:
In the quest to better understand the complex interactions between the multiple components of the immune system and cancerous cells, mathematical models can be used to address specific questions regarding disease progression, immune activation, and pathologies. The challenge is to find a balance between making models tractable and making models realistic. A good model answers important questions accurately. In this session, we will bring together applied mathematicians working in the area of tumor-immune dynamics, disease progression, and treatment to present their up-to-date research in the topic.

Intended Audience: Mathematicians, experimentalists, computational scientists, clinical researchers.
Schedule:

- **Tumor immune dynamics and the role of macrophages in tumor progression**
  Nicoline den Breems
  3:00 - 3:20

- **Modeling the effectiveness of therapeutic cancer vaccines: an agent-based approach**
  Adarsh Kumbhari
  3:20 - 3:40

- **Mathematical Systems Pharmacology Model of Immune Checkpoint Therapies to Optimize Mono- and Combination Treatment Regimens and Identify Potential Patient-Specific Biomarkers**
  Oleg Milberg
  3:40 - 4:00

- **Modelling diffusion of anti-cancer viruses in solid tumours**
  Pantea Pooladvand
  4:00 - 4:20

- **Mathematical Modeling of Malignancy in Bone Marrow and Peripheral Blood: Role of Cancer Stem Cells**
  Rachid Ouifki
  4:20 - 4:40
Tumour immune dynamics and the role of macrophages in tumour progression.

Nicoline den Breems*, Department of Mathematics, The University of Auckland, Auckland, New Zealand  
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Raluca Eftimie, Department of Mathematics, University of Dundee, Dundee, Scotland, r.a.eftimie@dundee.ac.uk

The immune system has been documented to play a role in tumour control for more than a century and resulted in the development of immune therapies to combat cancer. Some types of immune therapies have shown success but many anti-tumour immune therapies do not show the expected results. The immune-editing hypothesis emphasizes the dual role of macrophages in the immune response with M1 macrophages tumour-promoting and M2 macrophages tumour-suppressing. However, experimental studies have shown contradicting results. Understanding of the biological mechanisms governing the immune tumour interactions is far from complete but known to be complex, involving many non-linear interactions. Mathematical biology and the tools in this field are ideally suited to complement experimental studies and analyse the complex non-linear interactions. We developed an ODE model to analyse the role of macrophages in the tumour immune interactions.
Title: Impact of T cell avidity on cancer vaccines: an agent based approach

Abstract:
Therapeutic cancer vaccines treat cancers that have already developed by stimulating special cancer killing cells known as cytotoxic T cells. Despite showing promise, positive clinical outcomes have yet to be realized and a possible reason is due to the functional avidity of the T cell response. Vaccines elicit a low-avidity (i.e., weakly tumor-killing) T cell response, and the mere presence of low-avidity T cells can inhibit cancer killing by high-avidity T cells. By considering this “high-low interference” explicitly, we use a probabilistic agent-based model to explore what the optimal vaccination strategy is.
Mathematical Systems Pharmacology Model of Immune Checkpoint Therapies to Optimize Mono- and Combination Treatment Regimens and Identify Potential Patient-Specific Biomarkers

Oleg Milberg¹, Chang Gong¹, Bing Wang², Paolo Vicini³, Rajesh Narwal⁴, Lorin Roskos⁴, and Aleksander S. Popel¹
¹Departments of Biomedical Engineering and Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland; ²MedImmune, Mountain View, California; ³MedImmune, Cambridge, United Kingdom; ⁴MedImmune, Gaithersburg, Maryland

The advent of immunotherapy has brought about a new era of cancer treatment, one that promises great potential for tumor eradication. In order to reap the full benefits of such therapies, it is necessary to understand how they function in each patient and optimize how the therapies can be administered for the greatest responses. With this goal, we have developed a mathematical multiscale systems pharmacology model that would allow us to explicate in silico potential biomarkers for the identification of patients who would benefit most from particular types of immunotherapies, and optimally predict therapeutic regimens for those patients.

The model focuses on the molecular, cellular and tissue level changes that would occur during an immune response against a tumor, with a particular focus on the activities of immune checkpoint inhibitors against PD-1, PD-L1 and CTLA-4, administered as mono- or combination therapies. The model incorporates experimentally determined receptor binding constants, and cellular and molecular dynamics, as well as various cell types and states, including a heterogeneous tumor representation (for checkpoint receptor expression). In total, the model comprises of approximately 400 molecular and cellular species, and a mix of about 200 algebraic equations, 300 ODEs, and several discontinuous equation sets. Parameters were chosen to simulate the treatment of NSCLC and melanoma; although the framework is flexible enough to model other types of cancers, given their respective parameters. While the model is large, it has ample literature support quantitatively and qualitatively, with parameters mostly reflecting experimental and clinical values.

Qualitatively, the model identifies the pharmacokinetics of the immune checkpoint inhibitors in a manner consistent with previous studies, and additionally predicts the effects of those therapies on tumor response with results mirroring those reported from several published clinical trials. This includes the dose responses of the therapies in relation to their pharmacodynamic effects. In a quantitative manner, cellular densities, molecular expression levels, and T cell clonality levels differentiating therapy responders from non-responders are very similar to those reported in the literature. Future studies will allow statistical analyses of virtual population cohorts for further qualitative and quantitative confirmation of the generated results, and more refined predictions. Supported by grants from MedImmune and NIH R01CA138264.
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Title:
Modelling diffusion of anti-cancer viruses in solid tumours

Abstract:
One of the biggest barriers in treating solid tumours is the inability of the therapeutic vectors to propagate throughout the tumour mass due to the high density of the tumour and tumour stroma. The dense nature of many solid tumours can be attributed to a gel-like substance known as the extracellular matrix (ECM). This thick and compact structure acts as a physical barrier by shielding the malignant cells and reducing drug penetration and efficacy. One method to tackle the over-expression of ECM in solid tumours, is by using a relaxin-expressing adenovirus designed to degrade the ECM within the tumour, thereby increasing the effectiveness of the oncolytic virus. In this presentation, we explore this problem by introducing a system of reaction-diffusion PDEs, including tumour cells and anti-tumour viruses. Mimicking the heterogeneous environment observed in solid tumours, we aim to model the dynamics of ECM degradation and the subsequent effect on the malignant cells due to changes in drug penetration and diffusion.
Mathematical Modeling of Malignancy in Bone Marrow and Peripheral Blood: Role of Cancer Stem Cells.

Rachid Ouifki* (Rachid.Ouifki@up.ac.za) - Department of Mathematics and Applied Mathematics, University of Pretoria, South Africa

Evans K. Afenya - Department of Mathematics, Elmhurst College, 190 Prospect Avenue, Elmhurst, IL 60126 USA

In this presentation we develop and analyse a mathematical model that considers hematopoietic dynamics in the diseased state of the bone marrow and peripheral blood, alongside the cancer stem cell population. The proposed model consists of a system of five differential equations with two delays. Model analyses and simulations suggest that the emergence of the cancer stem cell population provides an aberrant environment in which the malignant population in the bone marrow could keep expanding even at equilibrium. Most notably, the stability analysis reveals that the mere existence of the cancer stem cell population tends to enhance and stimulate the expansion of non-stem malignant clones not only temporally but also at equilibrium and the converse also happens. This suggests that the cancer stem cell population is very crucial and critical in propagating malignancy.
Title: Synchrony across space in ecology: mathematical issue, challenges, and progress

Organizer: Alan Hastings
Environmental Science and Policy
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Summary:
Understanding the causes and consequences of synchrony across space is an important and long-standing issue in ecology. The implications range from the importance of synchrony for extinction and persistence across space to the role of synchrony (essentially spatial population dynamics) as a way to get a deeper understanding of what determines population dynamics. From a mathematical point of view intriguing aspects of dynamical systems are central to synchrony. On the mathematical side issues of synchrony can be traced back at least as far as the clocks of Christian Huygens and the area continues to be a very active area of research. Although the minisymposium focuses on ecology, issues of synchrony arise across mathematical biology including neuroscience and cell biology. The speakers will discuss both a range of ecological problems as well as a range of mathematical approaches. The causes of some of the most dramatic cases of synchrony in ecology – the dynamics of periodical cicadas and the masting of plants – are still not understood. The speakers will discuss both classical approaches based on coupled oscillators to new approaches based on ideas from statistical physics as well as applications using a variety of mathematical descriptions including integro-difference equations.
Schedule:

- *Ecological Synchrony: An overview from weakly coupled systems to the Ising model*
  Alan Hastings*, Andrew E. Noble, Patrick H. Brown, Todd S. Rosenstock, Jonathon Machta
  3:00 - 3:30

- *Uncovering the drivers of spatial synchrony of periodical cicadas in the U.S.*
  Julie Blackwood*, Alan Hastings, Andrew Liebhold, Jonathan Machta, Andrew Noble
  3:30 - 4:00

- *Dispersal-driven phase-amplitude asynchrony across ecosystems*
  Frederic Guichard*, Yuxiang Zhang, Julien Mass-Jodoin, Frithjof Lutscher
  4:00 - 4:30

- *Masting of trees: coupled chaotic systems tested by long-term flowering data*
  Yoh Iwasa*, Akiko Satake
  4:30 - 5:00
A. Authors

*Alan Hastings (Environmental Science & Policy, UC Davis, amhastings@ucdavis.edu)

Andrew E. Noble (Environmental Sci. & Policy, UC Davis, andrewenoble@gmail.com)

Patrick H. Brown (Plant Sciences, UC Davis, phbrown@ucdavis.edu)

Todd S. Rosenstock (World Agroforestry Centre, T.Rosenstock@cgiar.org)

Jonathon Machta (Physics, University of Massachusetts, machta@physics.umass.edu)

B. Title and Abstract

Title: Ecological Synchrony: An overview from weakly coupled systems to the Ising model

Abstract: Synchrony of periodic dynamics across space is a dramatic ecological phenomenon. We will begin with an overview of both the phenomena and classical mathematical approaches which range from simulations to studies of weakly coupled systems. A central question in ecology is the degree to which the spatial synchrony of oscillating populations is explained by endogenous forcing, related to coupling and local dynamics, versus exogenous forcing, known as the Moran effect. By applying ideas from statistical physics originally used to explain the behavior of magnets to a data set on yield from pistachio trees, we work towards a robust description and potential explanation for the generation of spatial synchrony in ecology. We show, using 5 years of data on over 6,500 trees in a pistachio orchard, that annual nut production, in different years, exhibits either large-scale synchrony or self-similar, power-law decaying correlations corresponding to the Ising model near criticality. Our approach suggests looking for novel mechanistic underpinnings that lead to synchrony and a surprising correspondence between the description of a physical phenomena, magnetization, and ecological dynamics.
A. Authors

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Jonathan Machta, University of Massachusetts, Amherst, machta@physics.umass.edu

Andrew Noble, GNS Healthcare, andrewenoble@gmail.com

B. Title and Abstract

Title: Uncovering the drivers of spatial synchrony of periodical cicadas in the U.S.

Abstract: In addition to their unusually long life cycle, periodical cicadas provide an exceptional example of synchronized life stage phenology in nature. Single broods (or age cohorts) span large geographical regions ranging from 50,000 to 500,000 km², and adults emerge synchronously every 13 or 17 years. The mechanisms driving the observation that only a single brood is normally present in a given spatial location remain largely unknown. We develop non-linear Leslie matrix-type models of periodical cicadas that include predation-driven Allee effects and competition in addition to reproduction and survival. We use our models to lend insight into the driving forces behind the observed spatial structure of periodical cicadas.
A. Authors

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Frithjof Lutscher (University of Ottawa, flutsche@uottawa.ca)

B. Title and Abstract

Title: Dispersal-driven phase-amplitude asynchrony across ecosystems

Abstract: Spatial synchrony has become a central phenomenon to infer mechanisms driving species coexistence and ecosystem function. Metrics of spatial synchrony includes statistical correlation or phase difference between time series in relation to geographic distance. However, it is not even clear how asynchrony, or deviation from synchrony, should be defined. We will start from synchrony defined by the stability of a fixed phase difference between time series, thus including in-phase or any phase-locked state. We sill study asynchrony as the emergence of non-equilibrium dynamics in phase equations. Using the Rosenzweig-MacArthur predator-prey model, we will first derive the minimum conditions for self-sustained spatial asynchrony driven by weak dispersal in a trophic metacommunity. The model is analyzed using phase dynamic equations for weakly coupled oscillators and numerical simulations of the full metacommunity model. Our analysis demonstrates that the loss of synchrony among homogeneous and weakly coupled communities is only possible in systems of at least 3 patches. More specifically, we show that pulse-relaxation predator-prey dynamics leading to stable phase-locked dynamics between 2 patches switch to asynchronous dynamics in a 3-patch metacommunity where weak dispersal causes the frequency of oscillations in each patch to fluctuate through time. Finally, we show that coupled phase-amplitude dynamics can generalize dispersal-driven phase asynchrony to asynchrony of both phase and amplitude under strong coupling. We discuss the implications of our results for the interpretation of ecological data that exhibit non-stationary statistical correlation or phase-amplitude dynamics among locations or species.
A. Authors

*Yoh Iwasa (Department of Biology, Kyushu University, yohiwasa@kyudai.jp)

Akiko Satake (Department of Biology, Kyushu University, akiko.satake@kyudai.jp)

B. Title and Abstract

Title: Masting of trees: coupled chaotic systems tested by long-term flowering data

Abstract: Trees in mature forests often show intermittent reproduction. Intensive flowering and seed production occur only once in several years, often synchronized over a long distance. We study a coupled map model for the dynamics of energy reserve of individuals, and show that trees become synchronized in reproduction if their fruit production is limited by the availability of outcross pollen. We then examine a coupled map lattice with local pollen exchange and condition for a strong synchronization over the whole forest to develop from rather short range pollen exchange. We also discuss the reproductive synchronization between different species which share common pollinators. Finally we report an exploration of the proximate mechanism of masting by combining spatiotemporal flowering data, biochemical analysis of resource allocation, and mathematical modeling. Flowering data of 170 trees over 13 years showed the emergence of clustering with trees in a given cluster mutually synchronized in reproduction, as predicted by the model. A fully parameterized model demonstrated that the observed flowering pattern is explained only when the interplay between nitrogen dynamics and climatic cues was considered.
Liver as a model system for mechanics, flow, and multiscale mathematical biology

Paul Macklin, Department of Intelligent Systems Engineering, Indiana University
Bloomington, IN (macklinp@iu.edu)

Abstract:
The liver is a critical organ in human physiology, responsible for filtering harmful products in the bloodstream and secreting bile. It is the only organ that can regenerate, but it is susceptible to toxic damage, viral infection (hepatitis), scarring (cirrhosis), primary and metastatic cancer, and failure. The liver is an excellent model system to drive advances in mathematical and computational systems biology, due to its dynamical coupling between multiple biophysical processes at several scales, including intracellular signaling and metabolism, bio-transport, biomechanics, interstitial and vascular flow, microenvironment-dependent phenotypes, and multicellular processes.

After introducing key liver biology for non-specialists in a 5-minute primer, this minisymposium will explore advances across 3-D computational systems biology, including virtual toxicology, coupling fluid flow and biomechanics in liver sinusoids, colon cancer metastatic growth in large liver tissues, and cancer response to nano-therapy. The talks will encompass lattice and off-lattice discrete models, multiple continuum models, and hybrid approaches. After a talk on high-throughput bioengineered experiments that can drive hypotheses, calibration, and model validation, we will close with a panel discussion on the next steps to producing comprehensive simulation frameworks for the multiscale, multi-physics processes inherent to biology.
Schedule:

- **Primer: Liver microanatomy and biology for modelers**  
  Paul Macklin  
  10:30 - 10:50

- **Sensitivity analysis of toxicity of acetaminophen in a multiscale liver sinusoid simulation**  
  James A. Glazier  
  10:50 - 11:10

- **Biomechanical modeling of tissue perfusion in decellularized and native liver**  
  Jessica Sparks  
  11:10 - 11:30

- **Agent-based simulation of colon cancer metastases in large liver tissues**  
  Paul Macklin  
  11:30 - 11:50

- **Modeling and calibration of cancer drug response**  
  Hermann B. Frieboes  
  11:50 - 12:10

- **High-throughput image-based experiments to drive cancer model development**  
  Shannon M. Mumenthaler  
  12:10 - 12:30
Liver as a model system for mechanics, flow, and multiscale mathematical biology

Paul Macklin, Department of Intelligent Systems Engineering, Indiana University
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Abstract:
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Primer: Liver microanatomy and biology for modelers

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Paul Macklin*, Department of Intelligent Systems Engineering, Indiana University
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Shannon M. Mumenthaler, Lawrence J. Ellison Institute for Transformative Medicine, University of Southern California; Los Angeles, CA (smumenth@usc.edu)

Jessica L. Sparks, Department of Chemical, Paper and Biomedical Engineering, Miami University
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(* denotes presenter)

Abstract:
In this talk, we briefly outline the key features in liver microanatomy, including the microarchitecture and function of liver sinusoids and lobules, interstitial and microvascular flow, and associated clinical problems in toxicology and cancer. This 5-minute primer will provide the necessary biological background for the entire minisymposium.
Analysis of toxicity of acetaminophen in a multiscale liver sinusoid simulation

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James Klaunig, School of Public Health, Indiana University; Bloomington, IN (j klauni@Indiana.edu)

(* denotes presenter)

Abstract:
Acetaminophen (APAP) overdose causes many thousands of deaths in the USA every year due to liver failure. The primary mechanism of liver damage is production of the metabolite NAPQI through Phase I metabolism in hepatocytes (especially through Cytochrome P450 2E1, but also through a number of other cytochromes). NAPQI binds irreversibly to Glutathione, a buffer of reactive oxygen species and depletion of Glutathione in turn leads to rapid cell death via necrosis. While the liver has great powers of regeneration under many circumstances, the particular pattern of cell death due to APAP poisoning often leads to necrosis of the entire liver rather than recovery. Because many factors including within population variability, age, state of health, consumption of alcohol, medications and some foods can significantly alter the pattern of cytochrome expression within individual hepatocytes, doses of APAP tolerated in a typical individual can be toxic in susceptible subpopulations and doses previously tolerated in a given individual may be toxic after exposure to particular modulators of cytochrome production. We have developed a three-scale virtual-tissue simulation in the open-source CompuCell3D simulation environment, which includes a PBPK model of whole body dosimetry and partitioning after ingestion of APAP, a multicell model of a simplified liver sinusoid including transport of Acetaminophen in the blood and its uptake by hepatocytes and a subcellular SBML reaction-kinetic model of APAP metabolism and NAPQI production in each hepatocyte. We validated a baseline set of parameters by tuning to reproduce clinically-measured serum concentration time-series of APAP and its metabolites, then systematically investigated the sensitivity of the maximum degree of Glutathione depletion on model parameters, providing preliminary insights into factors contributing to population variability in APAP toxicity. We also discuss the effects of liver architecture on the microdosimetry of APAP.
Biomechanical modeling of tissue perfusion in decellularized and native liver

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Jessica L. Sparks*, Department of Chemical, Paper and Biomedical Engineering, Miami University  
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(* denotes presenter)

Abstract:
Regenerative medicine has the potential to alleviate severe donor organ shortages for patients with end-stage liver failure. Bioengineered liver constructs could also serve as test platforms for pharmaceutical research, liver disease, metastasis, and development. Organ decellularization, a promising bioscaffolding technique, is the removal of all cellular components from an organ leaving behind intact extracellular matrix (ECM). Since the vasculature is retained, decellularized scaffolds have the potential to generate bioengineered liver constructs at the whole-organ scale. Scaffold perfusion through a cannulated portal vein generates a variety of mechanical forces that act across multiple length scales, from pressure and shear stress in vascular channels to interstitial flow and ECM tension in the parenchyma. Since many liver cell types, including hepatic stem/progenitor cells, hepatocytes, endothelial cells, stellate cells, cholangiocytes, and portal fibroblasts, are sensitive to mechanical stimuli, we hypothesize that providing optimal biomechanical conditions inside the scaffold is important for successful generation of viable tissue. Currently little is known about the biomechanical environment in decellularized tissue. The goal of this research is to quantify the mechanical microenvironment in decellularized liver, for varying organ-scale perfusion conditions, using a combined experimental/computational approach. Needle-guided ultra-miniature pressure sensors were inserted into liver tissue to measure parenchymal fluid pressure ex-situ in portal vein-perfused native (n=5) and decellularized (n=7) ferret liver, for flow rates from 3-12 mL/min. Pressures were also recorded at the inlet near the portal vein cannula. Experimental results were fit to a multiscale computational model to simulate perfusion conditions inside native versus decellularized livers for all flow rates. The multiscale model consists of two parts: an organ-scale electrical analog model of liver hemodynamics and a tissue-scale model of pore fluid pressure, pore fluid velocity, and solid matrix stress throughout a 3D hepatic lobule. Distinct models were created for native versus decellularized liver. Results show that vascular resistance decreases several fold as a result of decellularization. Similarly, the hydraulic conductivity of decellularized liver, a measure of tissue permeability, was approximately 5 times that of native liver. In future this modeling platform can be used to guide the optimization of biomechanical conditions in decellularized scaffolds for liver bioengineering. In ongoing research, this model is being applied to study flow patterns in liver lobules with tumor obstructions.
Agent-based simulation of colon cancer metastases in large liver tissues

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Paul Macklin*, Department of Intelligent Systems Engineering, Indiana University
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(* denotes presenter)

Abstract:
The liver is a common metastasis site for many cancers, especially breast, lung, and colorectal cancer (CRC). Beyond the complexities of tumor cell extravasation to seed new metastases, tissue biomechanics, growth substrate biotransport, porous flow, and tumor-host (parenchymal) cell interactions all shape the growth dynamics of newly seeded metastases. In this talk, we build mechanical and transport constitutive relations based upon detailed poroviscoelastic simulations of single liver lobules, allowing us to build agent-based simulations of square centimeter-scale liver tissues with hundreds of liver lobules. Using this simulation framework, we seed CRC metastases in the virtual liver, explore the impact of different hypotheses on tumor-parenchymal interactions, and discuss future model refinements to better match experimental and clinical observations. This work illustrates that the ordinary model of using agent-based simulations to learn constitutive relations for continuum models can be reversed: detailed continuum models can drive simplifications that make large-scale discrete simulations feasible. Our work is built upon the open source packages BioFVM and PhysiCell, and it will be released as open source at http://MathCancer.org.
Modeling and calibration of cancer drug response

Louis T. Curtis, The Ohio State College of Medicine; Columbus, OH (ltcurt11@gmail.com)
Hermann B. Frieboes*, Department of Bioengineering, University of Louisville
Louisville, KY (hbfrie01@louisville.edu)

(* denotes presenter)

Abstract:
Cancers are typically complex, multicellular tissues, and interactions between different cell types and their environment may become even more complex upon treatment. Components contributing to the tumor growth and treatment response include cancer and vascular endothelial cells, immune system and stromal cells, extracellular matrix, and the cellular microenvironment. Interactions within the tissue occur across a wide range of physical scales, from the molecular (nanometer) to the tissue (centimeter) scale. These components and their interactions can significantly affect cancer cell survival and eventually lead to the emergence of drug resistance. Conventional chemotherapy targets single cancer cell populations with drug doses and administration frequencies determined by the maximum tolerated dose to avoid lethal patient toxicity. Nanotherapies aim to enhance targeting of tumor tissue while minimizing toxic side effects. However, the large number of combinational protocols specifying the targeting of multiple tumor cell populations and their microenvironment by chemotherapeutic agents in concomitant or sequential administration may preclude determination of potential clinical options solely through experimental effort. This assessment would benefit from methods and principles typically used in systems analysis, such as in engineering and mathematics. We have employed mathematical modeling and computational simulation to simulate tumor response to conventional as well as nanoparticle-based drug regimens. We develop calibration methods to set model parameters based on experimental data in order to project potential response in vivo. This work represents a step towards the development of a comprehensive virtual system to evaluate tumor drug response, with the goal to more efficiently identify optimal course of treatment with patient tumor-specific data. Future model evaluation of chemotherapy possibilities may help to assess their potential value to obtain sustained tumor regression for particular patients, with the ultimate goal of optimizing the cancer drug response.
High-throughput image-based experiments to drive cancer model development

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(* denotes presenter)

Abstract:
Understanding metastatic spread to distant sites is one of the most challenging areas in cancer research today; yet it remains a difficult process to study in the laboratory largely due to discrepancies between cell culture models and tumor growth in vivo. Therefore, we are challenged with creating a reproducible and controllable experimental system that approximates in vivo conditions in order to probe the dynamics of cancer progression. Here we discuss the development of high throughput imaging techniques coupled with computational models to allow one to systematically investigate the relationships between tumor growth dynamics and heterogeneous microenvironments within bioengineered living tissue. We implement tools such as image segmentation, automated model-fitting, and machine learning to simultaneously characterize heterocellular phenotypes in response to relevant, co-occurring environmental stimuli. Specifically we highlight the differences in colon tumor cell behavior and response to therapy in standard tissue culture conditions versus a novel liver scaffold model, which better mimics the in vivo milieu. This image-based platform permits direct observation of cell population dynamics within precisely controlled environments that can be faithfully recapitulated in computational models of cancer progression.
MS11: Vector-Borne Diseases: What have we learned from them since the discovery of Malaria to the present

Minisymposium Title:

Vector-Borne Diseases: What have we learned from them since the discovery of Malaria to the recent emergence of the Zika Virus?

Organizers:

Folashade Agusto
Olivia Prosper
Miranda Teboh-Ewungkem

Summary:

From the discovery of the mode of transmission of malaria in the 1900s to the 2014 emergence of the Zika virus, it is clear that vector-borne diseases require our attention. The vertebrate host and vector populations each have their own population dynamics and are connected by disease-causing pathogens, whose success depends on both populations. Understanding the interactions that allow for successful disease transmission is a critical goal, and a necessary step for designing effective and practical methods to hamper their success. In this session, we bring together researchers working on vector-borne diseases with the aim to (1) share recent developments and findings in this area of research; (2) incite questions that could lead to new explorations; (3) ignite and foster the passion for others to get involved in research in this area and in the areas linking mathematics, biology and ecology.
Schedule:

- **Modeling and control of West Nile virus: Incorporating avian stage-dependent vector exposure**
  Suzanne Robertson
  10:30 - 11:00

- **Spatial dynamics of vector-borne diseases**
  Omar Saucedo
  11:00 - 11:30

- **Granuloma Formation in Leishmaniasis: Mathematical Models**
  Nourridine Siewe*, Abdul-Aziz Yakubu, Abhay R Satoskar, Avner Friedman
  11:30 - 12:00

- **The impact of recruitment on the dynamics of an immunesuppressed within human-host mathematical model of the Plasmodium Falciparum parasite**
  Woldegerima Assefa Woldegebrila, Miranda I. Teboh-Ewungkem*, Gideon A. Ngwa
  12:00 - 12:30
Modeling and control of *West Nile virus*: Incorporating avian stage-dependent vector exposure

Suzanne Robertson, Department of Mathematics and Applied Mathematics, Virginia Commonwealth University, srobertson7@vcu.edu

*West Nile virus* (WNV) is a major public health concern in the United States. While seasonal WNV outbreaks have been widely observed to be associated with the end of the avian nesting season, the ecological mechanisms determining this synchronicity are poorly understood. Newly hatched birds, or nestlings, have less feather coverage and fewer defense mechanisms than older birds, rendering them more vulnerable to mosquitoes. While total avian population size increases throughout the season, nestling abundance declines at the end of the brooding season. We investigate how this temporal variation in host stage abundance may structure enzootic WNV transmission with a mathematical model incorporating avian (host) stage-structure and within-species heterogeneity in the form of stage-specific mosquito (vector) biting rates. We determine the extent to which temporal fluctuations in host stage and vector abundance throughout the season, along with the differential exposure of these stages to mosquito bites, affects the timing and magnitude of WNV activity as well as implications for public health interventions. Specifically, we explore the viability of nestling vaccination as a new form of control in addition to the currently used controls of mosquito larvicide and adulticide.
Spatial dynamics of vector-borne diseases

Omar Saucedo*, Mathematical Biosciences Institute, The Ohio State University, Saucedo.10@mbi.osu.edu

Joseph Tien, Department of Mathematics, The Ohio State University, tien.20@osu.edu

Vector-borne diseases affect approximately 1 billion people and account for 17% of all infectious diseases. With travel becoming more frequent across the global, it is important to understand the spatial dynamics of vector-borne diseases. Host movement plays a key part on how a disease can be distributed as it enables a pathogen to invade a new environment, and helps the persistence of a disease in locations that would otherwise be isolated. In this talk, we will explore how spatial heterogeneity combines with mobility network structure to influence vector-borne disease dynamics.
Granuloma Formation in Leishmaniasis: Mathematical Models

Nourridine Siewe*, National Institute for Mathematical and Biological Synthesis (NIMBioS), nourridine@nimbios.org

Abdul-Aziz Yakubu, Department of Mathematics
Howard University, ayakubu@howard.edu

Abhay R Satoskar, Department of Microbiology, The Ohio State University, satoskar.2@osu.edu

Avner Friedman, Department of Mathematics The Ohio State University, afriedman@math.ohio-state.edu

Leishmaniasis is a disease caused by the Leishmania parasites. The two common forms of leishmaniasis are cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL). VL is the more severe of the two and, if untreated, may become fatal. The hallmark of VL is the formation of granuloma in the liver or the spleen. In this paper, we develop a mathematical model of the evolution of granuloma in the liver. The model is represented by a system of partial differential equations and it includes immigration of cells from the adaptive immune system into the granuloma; the rate of the influx is determined by the strength of the immune response of the infected individual. It is shown that parasite load decreases as the strength of the immune system increases. Furthermore, the efficacy of a commonly used drug, which increases T cells proliferation, increases in a person with stronger immune response. The model also provides an explanation why, in contrast to humans, mice recover naturally from VL in the liver.
The impact of recruitment on the dynamics of an immune-suppressed within human-host mathematical model of the Plasmodium Falciparum parasite

Woldegerima Assefa Woldegebriela, Department of Mathematics, University of Buea, Cameroon and AIMS Cameroon, and Department of Mathematics, Lehigh University, Bethlehem, PA.

Miranda I. Teboh-Ewungkem*, Department of Mathematics, Lehigh University, Bethlehem, mit703@lehigh.edu,

Gideon A. Ngwa, Department of Mathematics, University of Buea.

A deterministic framework is used to derive a system of autonomous nonlinear ordinary differential equations that describe the within human-host dynamics of the malaria parasite. Our model integrates known major actors involved in the development and progression of the disease, malaria, within the human body. The blood stage pathogenic asexual forms, the blood stage transmissible sexual forms of the parasite and mechanisms for the activation of the human immune response are included in the model development. We evoke some assumptions on the rate of production and depletion of healthy red blood cells and analyze the model under immune suppression. We show that the recruitment rate of healthy red blood cells has an impact on the model dynamics.
MS12: Modeling the dynamics of the cytoskeleton and associated motor proteins: gaining insight into the regulation of important cellular processes

**Title:** Modeling the dynamics of the cytoskeleton and associated motor proteins: gaining insight into the regulation of important cellular processes.

**Organizer:** Diana White, dtwhite@clarkson.edu

**Co-organizer:** Adriana Dawes, dawes.33@osu.edu

It is well known that cytoskeletal dynamics and organization, mediated by motor proteins, are directly linked to normal cell function, contributing to various cellular processes such as cell motility, polarization, and division. In this session, we focus on mathematical models that help to describe the dynamics and organization of various cytoskeletal components, as well as how these dynamics regulate specific cellular processes. Topics of discussion include models that accurately characterize MT dynamic instability, as well as models that describe myosin mediated contraction of actin networks. We will also discuss a model for clathrin-mediated endocytosis, which requires the coordination of various signals, cytoskeletal proteins, and molecular motors to successfully complete engulfment of cargo within a vesicle at the cell membrane. Further, models of the spatio-temporal distribution of intermediate filament vimentin will be discussed. Such models will be used to investigate the effects of motor protein driven transport and retrograde flow of actin on vimentin organization in cells. This session will highlight the varied mathematical approaches we can use to better understand fundamental cellular dynamics.
Modeling the dynamics of the cytoskeleton and associated motor proteins

Schedule:

- *Transport of intermediate filaments in astrocytes*
  Stephanie Portet*, John Dallon, Cecile Leduc, Sandrine Etienne-Manneville
  10:30 - 10:50

- *A Coarse-Grained Model of Clathrin-Coated Pit Nucleation during Clathrin-Mediated Endocytosis*
  Gillian L. Ryan*, Kiran H. Vekaria
  10:50 - 11:10

- *Behaviors of Steady-State Polymers Depend on Multiple Critical Concentrations*
  Ava Mauro*, Erin Jonasson, Chunlei Li, Shant Mahserejian, Ellen Norby, Jared Scripture, Mark Alber, Holly Goodson
  11:10 - 11:30

- *Modelling microtubule dynamic instability: applications to cancer chemotherapy*
  Diana White*, Florence Hubert, Stephane Honore
  11:30 - 11:50

- *Antagonistic motor protein dynamics in contractile ring structures*
  Adriana Dawes*, Valerie Coffman, Torah Kachur, David Pilgrim
  11:50 - 12:10
Transport of intermediate filaments in astrocytes

Vimentin is an intermediate filament protein expressed in astrocytes. The intracellular transport of vimentin assembled in filaments is one major determinant of the organization of intermediate filament networks in astrocytes. Based on experimental data, models of the spatio-temporal distribution of vimentin are developed to investigate the effects of motor proteins driven transport and retrograde flow of actin on the vimentin organization in cells. Furthermore, a model of transport of single filaments driven by motor proteins is also developed.
A Coarse-Grained Model of Clathrin-Coated Pit Nucleation during Clathrin-Mediated Endocytosis

Clathrin-mediated endocytosis (CME) is a common mechanism eukaryotic cells employ to internalize large cargo such as nutrients, hormones, and even viruses, and is the best-studied form of endocytosis. Successful CME requires bending the plasma membrane to completely engulf cargo within a vesicle, which in turn requires the coordination of various signals, cytoskeletal proteins, and molecular motors at the site of engulfment. A key precursor to successful CME is the formation of a clathrin-coated pit on the membrane. Experimental observations of the lifetimes of clathrin-coated pits in a plasma membrane using fluorescently-labeled clathrin have indicated that there exist two distinct subpopulations of clathrin-coated pits – those that lead to productive endocytosis events, and those that dissipate, or abort, before successful endocytosis may occur at that site. Examination of the fluorescent intensity of productive clathrin-coated pits indicates that these pits grow in a two-stage manner, with fast initial growth followed by a longer period of slow growth, with dynamic exchange of clathrin in the pits during both stages of growth. In this talk I will present a coarse-grained, stochastic model of clathrin-coated pit nucleation within the plasma membrane of a eukaryotic cell, and discuss the significance of the two clathrin pit subpopulations and the two-stage growth profiles within the context of the model.
Behaviors of Steady-State Polymers Depend on Multiple Critical Concentrations

The concept of critical concentration (CC) is a central idea in the study of microtubule assembly. Classically, the CC is accepted to be a single value with several equivalent definitions derived from understanding of equilibrium polymers, the most familiar being the idea that the CC is the subunit concentration needed to get polymer assembly. While this classical understanding can explain some aspects of microtubule behavior, it leaves other questions unresolved, including how to adjust the equilibrium theory to account for nucleotide hydrolysis, how to relate the CC to dynamic instability, and why the behavior of microtubules is so different from that of actin. We are using computational models of microtubule dynamics to address these questions and other problems related to microtubule polymerization behavior.
Modelling microtubule dynamic instability: applications to cancer chemotherapy

Questions regarding how microtubule targeting agents (MTAs), used in the treatment of a variety of cancers, alter microtubule (MT) dynamics have been investigated experimentally and theoretically. It has been well established that MTAs exert their cytotoxic effect on MTs by suppressing MT dynamic instability. However, at low non-cytotoxic levels, more interesting dynamics have been observed, such as an increase in MT dynamic instability. Also, it has recently been discovered that the end-binding (EB) family of tip tracking proteins sensitize the action of MTAs on MT dynamics in vitro [1] and in vivo [1,2].

Here, we propose a novel modelling approach, based on the work of Hinow et al. [3], to accurately describe MT dynamic instability in the presence of EBs. In particular, we develop an integro-partial differential equation model for MTs, that takes into account very large and fast shortening events that can be observed in such systems. For EBs, we introduce a pair of ODEs to describe the binding and unbinding of EBs with growing MT ends. From our model of MT dynamics, we define mathematical expressions for time- and distance-based catastrophe frequencies, which are used to compare simulation and experimental results. Simulation results illustrate that our model accurately describes MT dynamics for varying EB concentrations. Further, we show how our model can be used to suggest possible mechanisms for how EBs work to sensitize the action of MTAs on MT dynamic instability.

Antagonistic motor protein dynamics in contractile ring structures

Abstract: Ring-shaped contractile structures play important roles in biological processes including wound healing and cell division. Many of these contractile structures rely on motor proteins called myosins for constriction. We investigate force generation by the Type II myosins NMY-1 and NMY-2 using ring channels, contractile ring structures in the nematode worm C. elegans gonad that do not completely close, as our model system. By exploiting the ring channel’s circular geometry, we derive a second order ODE to describe the evolution of the radius of the ring channel. By comparing our model predictions to experimental depletion of NMY-1 and NMY-2, we show that these myosins act antagonistically to each other, with NMY-1 exerting force orthogonally and NMY-2 exerting force tangentially to the ring channel opening.
MS13: The Influence of Socio-Behavioral Mechanisms on the Spread of Newly
Emerging and Remerging Diseases

Mini-symposium Proposal
The Influence of Socio-Behavioral Mechanisms on the Spread of Infectious Diseases

Organizers:
1. Anuj Mubayi (School of Human Evolution and Social Change; Simon A. Levin Mathematical
   Computational Modeling Science Center, Arizona State University, Tempe, USA)
2. Anupama Sharma (Institute of Mathematical Sciences, Chennai, India)

The socio-behavioral factors (such as alteration in migration patterns, and change in
individual's behaviors in response to interventions) can drastically impact and shape the
epidemic trajectory. The focus of this mini-symposium will be on highlighting the importance
of this dimension in infectious diseases modeling and transmission dynamics. In today’s
time, where world is more connected than ever before, disease can spread across the world
in weeks. Hence, its imperative to have a holistic view of disease transmission to avoid any
disparities in the predicted and real outcome of epidemic, which may arise due to
heterogeneity of behavioral responses, mobility pattern and socio-economic status among
the population, as seen during recent H1N1 and Zika epidemics. The symposium will foster
the work in direction of developing data-driven models that capture this co-evolutionary
dynamics of behavioral and social determinants of infectious disease spread.
MS13
The Influence of Socio-Behavioral Mechanisms on the Spread of Infectious Diseases

Tuesday, July 18, 10:30–12:30, Officer’s Club North

Schedule:

- *Emergence of voluntary vaccination behavior in a population of rational agents*
  Anupama Sharma*, Shakti N. Menon, V. Sasidevan, Sitabhra Sinha
  10:30 - 11:00

- *Theoretical framework on time required for vaccinating a population: An example for H1N1*
  Arni S.R. Srinivasa Rao*, Tae Jin Lee, Thomas K
  11:00 - 11:30

- *Coupled effects of fever on host mobility and infectiousness: dengue as a data-driven case study*
  Kathryn Schaber
  11:30 - 12:00

- *Changes in air-travel-driven human mobility patterns and propagation of infectious diseases*
  Anuj Mubayi*, Matthew Scotch, Prashanth Rajagopal, Matteo Vaiente
  12:00 - 12:30
**Title:** Emergence of voluntary vaccination behavior in a population of rational agents

**Authors:** Anupama Sharma¹∗, Shakti N. Menon¹, V. Sasidevan², Sitabhra Sinha¹

¹The Institute of Mathematical Sciences, CIT Campus, Taramani, Chennai-600113, India
²Frankfurt Institute for Advanced Studies, 60438 Frankfurt am Main, Germany

e-mail: anupama@imsc.res.in(AS); shakti@imsc.res.in(SNM); sasidevan@gmail.com(VS); sitabhra@imsc.res.in(SS)

**Abstract:** Vaccination is a core component of Public health initiatives for preventing or containing an epidemic of a vaccine-preventable disease. Apart from protecting the individual receiving the vaccine from getting infected, large-scale vaccination also provides herd immunity to the population and is thus a public good. A major factor underlying the success of such an immunization program is the public perception about the benefits and costs associated with vaccination, especially when the decision to get vaccinated is a voluntary one (i.e., in the absence of coercion). Specifically, when the prevalence of a disease is low, the perceived risk of getting infected can be much lower than the perceived cost of getting vaccinated (in terms of side-effects or effort involved, apart from monetary), making the latter course of action less lucrative. With increasing prevalence, the perceived benefit of vaccination may eventually exceed the perceived cost, and as a result individuals will be more likely to opt for vaccination. From the point of view of a rational individual or agent, the best outcome will be one where everybody else gets vaccinated so that she enjoys the benefit of herd immunity, while not incurring any cost associated with getting vaccinated herself. However, if every individual argues in this manner, the vaccination drive will be unsuccessful and the population will be vulnerable to a large-scale epidemic. It is equivalent to the “free-rider” problem in game theory, where a choice that appears to be optimal for an individual will be sub-optimal if everyone adopts it. This problem lies at the heart of the phenomena of social dilemmas, such as the prisoners’ dilemma, which provides a natural framework for understanding voluntary vaccination behavior in a population of rational agents. We have introduced an integrated SIR model of epidemic spreading in a social network of rational agents. Unlike in previous models where agents copy the actions of “successful” neighbors, here individuals make a strategic decision on whether to get vaccinated based on information about disease prevalence (either local or global) and immunization status of neighbors. As the payoff matrix governing the decision process of agents evolves with the disease prevalence in the course of an epidemic, our model allows co-evolution of the vaccination behavior with the spreading of the contagion. We observe that voluntary vaccination can emerge spontaneously in response to an epidemic outbreak under certain circumstances. An important consideration is the source of information about the prevalence of the disease, viz., local or global. For less contagious diseases (i.e., with a small basic reproduction number \(R_0\)) use of local information results in a significant decrease in the total number of infected individuals. The implications of our results may point towards important factors that govern the efficacy of public health intervention schemes involving mass vaccination.
2. **Arni S.R. Srinivasa Rao** (arni2006@gmail.com), Augusta University, Augusta, GA  
**Collaborators:** Tae Jin Lee (Augusta University, Augusta, GA), Thomas K (Pondicherry Institute of Medical Sciences, Pondicherry, India)  
**Title:** Theoretical framework on time required for vaccinating a population: An example for H1N1.  
**Abstract:** In 2009 a new swine influenza virus (H1N1), emerged in Mexico and the USA. The virus quickly spread worldwide through human-to-human transmission. The propensity of the virus to primarily affect children, young adults and pregnant women, especially with some prior medical conditions, and the substantial increase in rate of hospitalizations, prompted the efforts of the scientific and pharmaceutical industry to develop H1N1 influenza vaccines. We theoretically understand the time required to vaccinate against viruses in the total population as well as sub populations in a country. We have proved novel theorems for the time functions defined in the paper. An example on H1N1 vaccination in India is provided.
The Influence of Socio-Behavioral Mechanisms on the Spread of Infectious Diseases

Tuesday, July 18, 10:30–12:30, Officer’s Club North

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Alex Perkins (taperkins@nd.edu), The University of Notre Dame

Title: Coupled effects of fever on host mobility and infectiousness: dengue as a data-driven case study

Abstract: Dengue virus (DENV) is a mosquito-borne pathogen that has been estimated to cause as many as 96 million clinical episodes of fever and other symptoms worldwide in a single year. At the same time, DENV is associated with roughly three-fold as many infections that result in either mild illness or no symptoms whatsoever. This mixture of symptomatic and asymptomatic DENV infections, combined with the complex ecology of its transmission, raise a number of questions about the dynamic feedback of fever and other symptoms associated with DENV infection onto its transmission dynamics. To understand the dynamic role of fever in DENV transmission dynamics, I will first present empirical results from a field study in Iquitos, Peru, that establishes a range of effects of DENV-associated fever on patterns of intra-urban human mobility. I will then present a model-based analysis of empirical data from field and laboratory studies that quantifies the relative infectiousness of individuals with fever and other symptoms as compared to those without any detectable symptoms. Together, these results highlight the importance of acknowledging the coupled nature of heterogeneities in host mobility and infectiousness for understanding the transmission dynamics of DENV and other pathogens.

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Anuj Mubayi (amubayi@asu.edu), Arizona State University-Tempe, USA
Collaborators: Matthew Scotch, Prashanth Rajagopal, Matteo Vaiente; (Arizona State University-Tempe)

Title: Changes in air-travel-driven human mobility patterns and propagation of infectious diseases

Abstract: The transmission and spread of infectious diseases are determined by complex interactions between the host (either humans or nonhuman hosts), vector (e.g. mosquito) and various pathogens. Information on global human movement patterns is central to spatial epidemiological models used to predict the behavior of influenza and other infectious diseases. Yet it remains difficult to test which modes of dispersal drive pathogen spread at various geographic scales using standard epidemiological data alone. In this project, we understand dynamic risk based surveillance map for infectious diseases based on human mobility data, demography, and entomological data collected from other reliable resources as well as a mathematical model.
Title: Modeling Transport and Control Processes in Systems Physiology

Organizer: Dr. Laura Ellwein-Fix (jellwein@vcu.edu)
Department of Mathematics and Applied Mathematics, Virginia Commonwealth University
Phone: 804-828-2748

Co-Organizer: Dr. Mette S. Olufsen (msolufse@ncsu.edu)
Department of Mathematics, North Carolina State University
Phone: 919-515-2678

Summary: The transport and control of biological fluids and metabolites is critical to human health, yet remain difficult to measure and subsequently quantify. Computational modeling provides a method for simulating dynamics of physiological transport to aid in understanding the bases of both health and disease. This minisymposium will focus on recent mathematical and computational models of transport and control processes describing phenomena including reactivity to orthostatic and metabolic challenges, blood-clotting, hemorrhagic shock, and respiratory instability, all potential features of physiological system morbidity.
Schedule:

- *Cardiovascular system blood flow and metabolic control in hemorrhagic shock*
  Brian Carlson*, D.A. Beard, B.M. McCracken, K.R. Ward
  10:30 - 11:00

- *Impact of chest wall compliance on respiration dynamics*
  Laura Ellwein-Fix, Henry Rozycki
  11:00 - 11:30

- *Toward a Computational Model of Hemostasis*
  Karin Leiderman
  11:30 - 12:00

- *Systems analysis of transport and control in the cardiovascular system*
  Mette Olufsen
  12:00 - 12:30
Title: Cardiovascular system blood flow and metabolic control in hemorrhagic shock

Brian Carlson* (bcarl@med.umich.edu), Beard DA\textsuperscript{1,4}, McCracken BM\textsuperscript{2,4}, Ward KR\textsuperscript{2,4}, Tiba MH\textsuperscript{2,4} and Lee JH\textsuperscript{3,4}

\textsuperscript{1} Molecular and Integrative Physiology, University of Michigan, Ann Arbor, USA
\textsuperscript{2} Emergency Medicine, University of Michigan, Ann Arbor, USA
\textsuperscript{3} Emergency Medicine, Seoul National University, Bundang Hospital, Gyeonggi-do, Korea
\textsuperscript{4} Michigan Center for Integrative Research in Critical Care (MCIRCC)

Treatment of hemorrhagic shock centers around halting bleeding and replacing lost blood volume. However, the differential physiological response of organs during hemorrhage and resuscitation are poorly understood. We used a combined porcine experimental and computational cardiovascular systems model to identify how cardiovascular system blood flow and metabolism is controlled during hemorrhagic shock. In this experimental study eleven animals were hemorrhaged removing 50-55% of blood volume and then resuscitated with whole blood in amount equal to shed blood. It was found from the experimental observations that baseline blood oxygen extraction (before hemorrhage) correlated well with a full return of cardiovascular function post resuscitation. In the eleven animals, six were found to have an oxygen extraction ration (OER) of less than 30% and five were greater than 30% at baseline. The high OER group showed low peak lactate in the blood and heart rates returning to normal in resuscitation which was indicative of successful resuscitation. The reason for this differential response could not be determined from the measurements alone therefore a lumped parameter cardiovascular system model consisting of a system of approximately 50 ODEs was used to understand the underlying physiological differences in cardiovascular system blood flow and metabolic control between these two groups.
Title: Impact of chest wall compliance on respiration dynamics

Laura Ellwein-Fix¹ (lellwein@vcu.edu), Henry Rozycki²

¹Department of Mathematics and Applied Mathematics, Virginia Commonwealth University, VA
²Neonatal Medicine, Children's Hospital of Richmond at VCU, Richmond, VA

Noninvasive ventilation is used for respiratory support in infants to avoid the complications of traditional ventilation associated with intubation and high pressures. It is often less successful in extremely low birthweight or premature infants who remain at significant risk for developing chronic lung disease. This has been attributed, in part, to their high chest wall compliance resulting from an underminerlized rib cage in early gestation. Progressive lung collapse and thus low oxygenation are observed within a few days as the forces needed to open airspaces after each exhalation become insufficient. We present a compartmental pressure-flow model of respiratory dynamics that demonstrates lung volume loss at high chest wall compliance. Nonlinear compliance relationships $V(P)$ reflect clinically acquired pressure-volume curves in variable-volume regions such as the lungs and chest wall. A probabilistic alveolar recruitment submodel takes into account the pressure dependence of the opening and closing of individual air sacs, and is integrated as a positive feedback process simulating the interaction between lung volume loss and inefficient inhalation. This model may be useful in designing methods to support the chest wall and permit noninvasive ventilation in these patients at high risk for chronic lung disease.
Title: Toward a Computational Model of Hemostasis

Karin Leiderman (kleiderman@mines.edu)

Department of Applied Mathematics and Statistics, Colorado School of Mines, CO

Hemostasis is the process by which a blood clot forms to prevent bleeding at a site of injury. The formation time, size and structure of a clot depends on the local hemodynamics and the nature of the injury. Our group has previously developed computational models to study intravascular clot formation, a process confined to the interior of a single vessel. Here we present the first stage of an experimentally-validated, computational model of extravascular clot formation (hemostasis) in which blood through a single vessel initially escapes through a hole in the vessel wall and out a separate injury channel. This stage of the model consists of a system of partial differential equations that describe platelet aggregation and hemodynamics, solved via the finite element method. We also present results from the analogous, in vitro, microfluidic model. In both models, formation of a blood clot occludes the injury channel and stops flow from escaping while blood in the main vessel retains its fluidity. We discuss the different biochemical and hemodynamic effects on clot formation using distinct geometries representing intra- and extravascular injuries.
The cardiovascular system transports blood throughout the body to ensure adequate perfusion of all organs. The system is tightly controlled by the autonomic system to ensure homeostasis. Cardiovascular diseases are among the most devastating and associated with high mortality. Most of these are caused by two major problems – remodeling of the cardiovascular environment and autonomic disorders. This study will discuss a number of factors that impact the systems using 0D and 1D models predicting blood flow and pressure in the cardiovascular system. Specific focus will be on showing how remodeling impact wave propagation and how the remodeled system responds to a given challenge such as postural or respiratory challenge.
MS15: Recent advances in modeling vector-borne disease transmission: improving our understanding of underlying mechanisms and implications for disease control

Organizer: Folashade Agusto, University of Kansas, fbagusto@ku.edu
Co-organizer: Olivia Prosper, University of Kentucky, olivia.prosper@uky.edu
Co-organizer: Miranda Teboh Ewungkem, Lehigh University, mit703@lehigh.edu

Title: Recent advances in modeling vector-borne disease transmission: improving our understanding of underlying mechanisms and implications for disease control.

Summary:
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, sandflies, and kissing bugs. According to the World Health Organization, vector-borne diseases constitute more than 17% of all 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. Thus, 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. Hence, in this session, we will consider three main vector-borne diseases of public health concern; namely, Zika virus, Trypanosoma cruzi and West-Nile virus. We will focus on different aspects of these diseases from emergence in a new region to a secondary mode of transmission to disease persistence and lastly to mechanisms driving the disease.
Schedule:

- *Estimating the reproductive number, total outbreak size, and reporting rates for Zika epidemics in South and Central America*
  Deborah Shutt, Carrie A Manore, Stephen Pankavich, Aaron T Porter, Sara Y. Del Valle
  10:30 - 11:00

- *Examining the effect of sexual transmission on the dynamics of Zika infection*
  Ondrej Maxian, Anna Neufeld, Emma J. Talis, Lauren M. Childs*, Julie Blackwood
  11:00 - 11:30

- *Escaping competitive exclusion through seasonality: T. cruzi co-persistence*
  Christopher Kribs* and Christopher Mitchell
  11:30 - 12:00

- *Oscillations and driving mechanisms in a model of West Nile virus with time delay*
  Guihong Fan, Chunhua Shan*, Huaiping Zhu
  12:00 - 12:30
**Title:** Estimating the reproductive number, total outbreak size, and reporting rates for Zika epidemics in South and Central America

Deborah Shutt\(^1\)*, Email dshutt@mymail.mines.edu
Carrie A Manore\(^2\,3\,4\)
Stephen Pankavich\(^1\)
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1 Colorado School of Mines
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5 Los Alamos National Laboratory, NM, USA.

**Abstract:**
As South and Central American countries prepare for increased birth defects from Zika virus outbreaks and plan for mitigation strategies to minimize ongoing and future outbreaks, understanding important characteristics of Zika outbreaks and how they vary across regions is a challenging and important problem. We developed a mathematical model for the 2015 Zika virus outbreak dynamics in Colombia, El Salvador, and Suriname. We fit the model to publicly available data provided by the Pan American Health Organization, using Approximate Bayesian Computation to estimate parameter distributions and provide uncertainty quantification. An important model input is the at-risk susceptible population, which can vary with a number of factors including climate, elevation, population density, and socio-economic status. We informed this initial condition using the highest historically reported dengue incidence modified by the probable dengue reporting rates in the chosen countries. The model indicated that a country-level analysis was not appropriate for Colombia. We then estimated the basic reproduction number, or the expected number of new human infections arising from a single infected human, to range between 4 and 6 for El Salvador and Suriname with a median of 4.3 and 5.3, respectively. We estimated the reporting rate to be around 16% in El Salvador and 18% in Suriname with estimated total outbreak sizes of 73,395 and 21,647 people, respectively. The uncertainty in parameter estimates highlights a need for research and data collection that will better constrain parameter ranges.
Title: Examining the effect of sexual transmission on the dynamics of Zika infection

Authors:
Ondrej Maxian\textsuperscript{1}, Anna Neufeld\textsuperscript{2}, Emma J. Talis\textsuperscript{3}, Lauren M. Childs\textsuperscript{4*}, Julie Blackwood\textsuperscript{2}

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Abstract:

The Zika virus (ZIKV) has captured worldwide attention with the ongoing epidemic in South America and its link to severe birth defects, most notably microcephaly. ZIKV is spread to humans through a combination of vector and sexual transmission, but the relative contribution of these transmission routes to the overall epidemic remains largely unknown. Furthermore, a disparity in the reported number of infections between males and females has been observed. We develop a mathematical model that describes the transmission dynamics of ZIKV to determine the processes driving the observed epidemic patterns. Our model reveals only a minor contribution of sexual transmission to the basic reproductive number, $R_0$. This contribution is too minor to independently sustain an outbreak and suggests that vector transmission is the main driver of the ongoing epidemic. While we find a small but intrinsic disparity between male and female case counts, the differences do not account for the vastly greater number of reported cases for females, indicative of a large reporting bias. Finally, we identify conditions under which sexual transmission may play a key role in sparking an outbreak, including temperate areas where ZIKV mosquito vectors are less prevalent.
Title: Escaping competitive exclusion through seasonality: T. cruzi co-persistence

Authors:
Christopher Kribs* (University of Texas at Arlington, kribs@uta.edu) and
Christopher Mitchell (University of Utah, chris.mitchell@hsc.utah.edu)

Abstract:
Simple deterministic models for transmission of Trypanosoma cruzi (Chagas disease) predict persistence of a single parasite strain, when multiple strains compete for access to hosts. So the observed co-persistence of two strains in some host populations at roughly equal levels begs an explanation. Since host sharing by vectors, and local stochasticity under habitat fragmentation, offer only partial explanations, this talk focuses on the role of seasonality in explaining co-persistence. We extend the notion of an invasion reproductive number to periodic epidemiological models, in order to apply it to seasonal transmission of T. cruzi.
Title: Oscillations and driving mechanisms in a model of West Nile virus with time delay

Authors:
Guihong Fan (Columbus State University, Georgia USA)
Chunhua Shan* (University of Toledo, Ohio USA, chunhuashan@gmail.com)
Huaiping Zhu (York University, Toronto, Ontario, Canada)

Abstract: West Nile virus is a typical vector-borne disease transmitted to humans or other animals by Culex mosquitoes. For the virus, avian birds serve as amplification hosts, yet vector mosquitoes play a critical role in the transmission and spread of the virus. To investigate the role of vector mosquitoes and the transmission dynamics of West Nile virus, we formulate a system of delay differential equations with a standard incidence rate to model the interaction between mosquitoes and birds. Dynamical analysis shows that the population of vector mosquitoes can force the system to oscillate, while incidental interaction between mosquitoes and birds would not cause oscillations. This result indicates that the population of vector mosquitoes is the fundamental driving factor for the oscillation in disease transmission when considering the impact of temperature.
Cancer develops in stages from incipience to metastasis, often followed by the emergence of drug resistance and evasion of the immune response. Understanding cancer progression and interaction with treatments will lead to insights into cancer therapy by aiding the design of innovative strategies that include and combine chemotherapy, virotherapy, immunotherapy, and other approaches.

Talks by students and researchers in mathematical biology will highlight ordinary and partial differential equations, integral equations, and agent-based models to capture the dynamics of cancer, cancer treatment, and anti-cancer immune responses. We will also highlight promising future research directions.
Schedule:

- *The role of microenvironment in regulation of cell infiltration in glioblastoma*
  Yangjin Kim*, Hans Othmer
  10:30 - 10:50

- *Flu viruses can be good viruses: mathematical modelling of viral infections as anti-cancer treatments*
  Adrianne Jenner*, Chae-Ok Yun, Peter Kim, Adelle Coster
  10:50 - 11:10

- *Mathematical modeling of oncolytic potency and reduced virus tumor-specificity in virotherapy*
  Khaphetsi Joseph Mahasa*, Amina Eladdadi, Lisette de Pillis, Rachid Ouifki
  11:10 - 11:30

- *Studying tumor-immune interaction with a multiscale systems biology model*
  Chang Gong*, Oleg Milberg, Bing Wang, Paolo Vicini, Rajesh Narwal, Lorin Roskos, Aleksander S. Popel
  11:30 - 11:50

- *Some Mathematical Modeling Perspectives on Cancer Prevention and Treatment*
  Evans Afenya*, Rachid Ouifki
  11:50 - 12:10
The role of microenvironment in regulation of cell infiltration in glioblastoma

Yangjin Kim *
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Malignant gliomas are the most common type of brain cancer, which arise from glial cells, and in their most aggressive form are called GBMs. GBMs are highly invasive and difficult to treat because cells migrate into surrounding healthy brain tissue rapidly, and thus these tumors are difficult to completely remove surgically. GIMs, which can comprise up to one third of the total tumor mass, are present in both intact glioma tissue and necrotic areas. They apparently originate from both resident brain macrophages (microglia) and newly recruited monocyte-derived macrophages from the circulation. Activated GIMs exhibit several phenotypes: one called M1 for classically activated, tumor suppressive, and another called M2 for alternatively activated, tumor promoting, and immunosuppressive. Within a tumor the balance between these phenotypes is typically shifted to the M2 form. Numerous factors secreted by glioma cells can influence GIM recruitment and phenotypic switching, including growth factors, chemokines, cytokines and matrix proteins. In this work, we focus on mutual interaction between a glioma and M1/M2 microglia mediated by CSF-1, TGF-beta, and EGF. Up-regulated TGF-beta leads to up-regulation of Smad within the tumor cells and secretion of MMPs, leading to proteolysis for EMT process and cell infiltration. The mathematical model consists of densities of glioma cells, M1 type cells, M2 type cells, and concentrations of CSF-1, EGF, TGF-beta, Extracellular matrix, and MMPs. We developed the model to investigate the mutual interactions between tumor cells in the upper chamber and microglia in the lower chamber. In the experiments, Boyden invasion assay was used to show that this mutual interaction induces glioma infiltration in vitro and in vivo. We show that our simulation results are in good agreement with the experimental data and we generate several hypotheses that should be tested in future experiments in vivo.

REF
Flu viruses can be good viruses: mathematical modelling of viral infections as anti-cancer treatments

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Viruses are small powerful infectious agents that straddle the divide between living and non-living. Once a virus infects a suitable living organism, such as a human, it can hijack the cells. The infected cell is then used to replicate the virus, which eventually bursts the cell, releasing thousands of new viruses. For some time now, the use of viruses as a potential anti-cancer agents has been of much interest in oncology. Through genetic modification, viruses can be forced to selectively infect, and replicate within, tumour cells, killing them in the process.

In this study we have derived a system of ODEs to describe the processes acting in this virus-tumour system. The model parameters, including viral burst size, viral burst rate and infectivity, were determined via simultaneous optimisation across multiple experimental data sets encompassing both in-vitro and in-vivo protocols. The sensitivity of the parameter values was assessed and the parameter space explored to determine the regions of applicability of the system.

From our optimised model we can infer the specific effects of different levels of genetic modifications of these viruses. The model also provides a platform from which we can explore and optimise the efficacy of different viral treatment and application modalities.
Mathematical modeling of oncolytic potency and reduced virus tumor-specificity in virotherapy

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Oncolytic virotherapy is an emerging cancer treatment modality that uses naturally occurring or genetically engineered viruses to destroy cancerous cells. However, this therapeutic approach faces many challenges including the immune system’s response to the virus and/or infected cells, which might impede the success of therapy. Additionally, clinical evidence indicates that some oncolytic viruses have the ability to infect and replicate within normal cells as well. While this could be seen as another challenge to virotherapy, it could be used to increase viral potency as long as the replication within normal cells is well understood and controlled. In the present paper we address by means of mathematical modeling the following question: How can oncolytic virus infection of some normal cells in the vicinity of tumor cells enhance oncolytic virotherapy? We formulate a mathematical model describing the interactions between the oncolytic virus, the tumor cells, the normal cells, and the antitumoral and antiviral immune responses. The model consists of a system of delayed differential equations with one (discrete) delay. We derive the model's basic reproductive number within tumor and normal cell populations and use their ratio as a metric for virus tumor-specificity. Numerical simulations are performed for different values of the basic reproduction numbers and their ratios to investigate potential trade-offs between tumor reduction and normal cells losses. A fundamental feature unravelled by the model simulations is its great sensitivity to parameters that account for most variation in the early or late stages of oncolytic virotherapy. From a clinical point of view, our findings indicate that designing an oncolytic virus that is not 100\% tumor-specific can increase virus particles, which in turn, can further infect tumor cells. Moreover, our findings indicate that when infected tissues can be regenerated, oncolytic viral infection of normal cells could improve cancer treatment.
Studying tumor-immune interaction with a multiscale systems biology model

Chang Gong * and Oleg Milberg
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Paolo Vicini (MedImmune, Cambridge, United Kingdom)
Rajesh Narwal and Lorin Roskos (MedImmune, Gaithersburg, Maryland, USA)

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Tumor development is commonly accompanied by the antitumor immune response, which is not always successful in eliminating tumors, leading to an equilibrium or tumor escape. Recent developments in cancer treatment demonstrated that this antitumor immunity can be harnessed and enhanced by therapeutics targeting human immune system, especially immune checkpoint modulators. However, vastly differential efficacy of such treatment among patients is observed and yet to be understood. The sheer complexity of this system calls for aid from computational and mathematical models.

We developed a systems biology model to characterize the interactions between cancer and immune cells during tumor development. The multiscale model consists an agent-based model as backbone on the tissue-cellular scale, where cancer and immune cells migrate on a three-dimensional lattice and react to their local environment. On the molecular scale, partial differential equations were employed to track the diffusion-degradation of cytokines released by cells into the microenvironment, which feeds back to influence behavior of cellular agents. We conceptualize immune response arising as a separate compartment connected to the tumor via lymphatic blood circulation.

Using this system, we can analyze the emergent behavior of tumor development in response to local and systemic factors. We are able to reproduce tumor development in the context of antitumor immunity, with or without immunotherapeutic intervention. The spatial explicit model allows spatio-temporal tracking of the evolvement of the tumor, which can be used to compare with both longitudinal and biopsy data from real patient. With parameter combinations reflecting patients with different neoantigen characteristics, such as mutational burden and antigen immunogenicity, our simulations generate a variety of pre-treatment patterns of PD1/PDL1 expression, which resemble observed tumor immuno-architectures in real patients. Our simulated treatment also shows that the percentage of PDL1 positive cancer cells which are not in the proximity of the tumor boundary or vasculature correlates with effective anti-PD1/anti-PDL1 treatment. The model provides a framework for discovering treatment/biomarker combinations in different cancer types based on cancer-specific experimental data.
Some Mathematical Modeling Perspectives on Cancer Prevention and Treatment

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The cancer prevention, detection, and treatment scorecard is discussed and placed in perspective. Mathematical approaches and techniques are used to investigate key results from recent clinical trials and recommendations are accordingly made.
MS17: Spatial Processes in Biology

Minisymposium on Spatial Processes in Biology

Organizers:
Samuel Isaacson, Department of Mathematics and Statistics, Boston University, isaacson@math.bu.edu
Jay Newby, Department of Mathematics, University of North Carolina, Chapel Hill, jaynewby@email.unc.edu

Summary:
A key component of biological models involving population processes is spatial transport of individuals (be they molecules, filaments, cells or organisms). Speakers in this session will present biological models in which capturing the spatial transport of individuals within a population is critical for understanding biological function. These models include the stochastic diffusion and reaction of proteins within cells, the movement and regulation of neurofilaments within axons, search processes by animals, and dispersal of insects by wind. While the biological applications are diverse, each of these problems involves the movement of individuals within a larger population, and related choices of whether to explicitly model individuals or use approximating continuous population fields.
Schedule:

- A nonlocal PDE model for axonal cytoskeleton segregation in neurodegenerative diseases
  Chuan Xue
  10:30 - 11:00

- A Stochastic Reaction-Diffusion Model for Enzymatic Reactions
  Samuel A. Isaacson, Ying Zhang*
  11:00 - 11:30

- Resource-Driven Encounters and the Induction of Disease Among Consumers
  Rebecca K Borchering, Steve E Bellan, Jason M Flynn, Juliet RC Pulliam, Scott A McKinley*
  11:30 - 12:00

- Inferring Stratified Parasitoid Wasp Wind Dispersal Mechanisms and Parameters from Coarse Data
  Christopher Strickland, Nadiah P. Kristensen, Laura A. Miller*
  12:00 - 12:30
Authors:
• Chuan Xue*, Ohio State University, cxue@math.osu.edu

Title:
A nonlocal PDE model for axonal cytoskeleton segregation in neurodegenerative diseases

Abstract:
The shape and function of an axon depend critically on the organization of its cytoskeleton, which is a dynamic system of intracellular polymers including microtubules, neurofilaments and actin. Under normal conditions, microtubules and neurofilaments align longitudinally in axons and are interspersed in axonal cross-sections. However, in many neurodegenerative disorders, they separate radially with microtubules clustered centrally and neurofilaments located near the periphery. This striking polymer segregation proceeds to focal accumulations of neurofilaments and/or organelles that are early hallmarks of nerve degeneration. Our detailed stochastic simulations suggested that this segregation is a consequence of the disruption of neurofilament transport along microtubules, and in the absence of neurofilament transport, axonal organelles pull microtubules to the center and displace neurofilaments to the periphery. Motivated by these results, we developed a nonlocal PDE model to systematically analyze how different balances of organelle transport and neurofilament transport affect the cross-sectional organization of microtubules and neurofilaments. In this talk, I will present results of the PDE model and the relation of the PDE model with the stochastic model.
Authors:
- Samuel A. Isaacson, Department of Mathematics and Statistics, Boston University, isaacson@math.bu.edu
- Ying Zhang*, Department of Mathematics and Statistics, Boston University, phzhang@bu.edu

Title:
A Stochastic Reaction-Diffusion Model for Enzymatic Reactions

Abstract:
Enzymatic reactions are a key component in signaling pathways. A large number of compartment-based ODE and stochastic models have been developed to investigate properties of such pathways over the past decade. In recent years, spatial-stochastic models have emerged as a more realistic representation for such processes. A variety of spatial stochastic models have been developed in the literature, among which lattice-based stochastic reaction-diffusion models are a popular approach for studying complex spatio-temporal processes inside cells. Chemical reactions in the most widely used lattice-based stochastic reaction-diffusion model, the reaction-diffusion master equation (RDME), are generally limited to molecules at the same lattice site. With this restriction, the RDME has several drawbacks in accurately resolving interactions at cellular scales. To more accurately represent such phenomena, we develop an accurate and convergent lattice-based stochastic reaction-diffusion model that allows reactions to occur through a variety of interaction mechanisms.
Authors:
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- Steve E Bellan, University of Georgia, steve.bellan@uga.edu
- Jason M Flynn, Tulane University, jflynn2@tulane.edu
- Juliet RC Pulliam, South African Centre for Epidemiological Modelling and Analysis, pulliam@sun.ac.za
- Scott A McKinley*, Tulane University, Mathematics, scott.mckinley@tulane.edu

Title:
Resource-Driven Encounters and the Induction of Disease Among Consumers

Abstract:
Territorial animals share a variety of common resources, which can be a major driver of conspecific encounter rates. We examine how changes in resource availability influence the rate of encounters among individuals in a consumer population by implementing a spatially explicit model for resource visitation behavior by consumers. Using data from 2009 and 2010 in Etosha National Park, we verify our model’s prediction that there is a saturation effect in the expected number of jackals that visit a given carcass site as carcasses become abundant. However, this does not directly imply that the overall resource-driven encounter rate among jackals decreases. This is because the increase in available carcasses is accompanied by an increase in the number of jackals that detect and potentially visit carcasses. Using simulations and mathematical analysis of our consumer-resource interaction model, we characterize key features of the relationship between resource driven encounter rate and model parameters. These results are used to investigate a standing hypothesis that the outbreak of a fatal disease among zebras can potentially lead to an outbreak of an entirely different disease in the jackal population, a process we refer to as indirect induction of disease.
Inferring Stratified Parasitoid Wasp Wind Dispersal Mechanisms and Parameters from Coarse Data

Abstract: Biological invasions have movement at the core of their success. However, due to difficulties in collecting data, medium- and long-distance dispersal of small insects has long been poorly understood and likely underestimated. The agricultural release of parasitic hymenoptera, a group of wasps that are critical for biological pest control, represents a rare opportunity to study the spread of insects on multiple spatial scales. Since these insects are typically less than 1 mm in size and are challenging to track individually, a first-time biocontrol release will provide a known spatial position and time of initial release for all individuals that are subsequently collected. In this paper, we develop and validate a new mathematical model for parasitoid wasp dispersal from point release, as in the case of biocontrol. The model is derived from underlying stochastic processes but is fully deterministic and admits an analytical solution. Using a Bayesian framework, we then fit the model to an Australian dataset describing the multi-scale wind-borne dispersal pattern of Eretmocerus hayati Zolnerowich & Rose (Hymenoptera: Aphelinidae). Our results confirm that both local movements and long distance wind dispersal are significant to the movement of parasitoids. The model results also suggest that flow velocity winds are the primary indicator of dispersal direction on the field scale shortly after release, and that average wind data may be insufficient to resolve long distance movement given inherent nonlinearities and heterogeneities in atmospheric flows. The results highlight the importance of collecting wind data when developing models to predict the spread of parasitoids and other tiny organisms.
MS18: Immunobiology and Infection Subgroup

**Immunobiology and Infection Subgroup**

Amber Smith, St. Jude Children’s Research Hospital, amber.smith@stjude.org

Judy Day, University of Tennessee, judyday@utk.edu

Jessica Conway, Pennsylvania State University, jmc90@psu.edu

**Overview:** 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 objective is to discuss various topics including

- infectious diseases within-host
- 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 inaugural symposium, we will highlight recent research in these areas and discuss our vision for the subgroup and the future of the field.
Schedule:

- *Introduction of the Subgroup*
  Jessica Conway
  10:30 - 11:00

- *Experimentally Validating Model Predictions to Define Mechanisms of Respiratory Infections*
  Amber Smith
  11:00 - 11:30

- *Tissue Damage as a Biomarker and Immune Stimulus in Inflammation Models*
  Judy Day
  11:30 - 12:00

- *Discussion on the Future of Mathematics in Immunobiology and Infection*
  Amber Smith, Judy Day, Jessica Conway
  12:00 - 12:30
Introduction to the Immunobiology and Infection Subgroup

Jessica Conway*, Pennsylvania State University, jmc90@psu.edu,
Judy Day, University of Tennessee, judyday@utk.edu
Amber Smith, St. Jude Children’s Research Hospital, amber.smith@stjude.org

The Immunobiology and Infection Subgroup was created to bring together researchers who are interested in the modeling and analysis of immune processes in human disease and of host-pathogen interactions. We will first introduce the subgroup and discuss our goals for this inaugural symposium. Following this introduction, we will have two talks that will provide an overview of some of the research areas of our Subgroup. These will lay the foundation from which we will launch a discussion and exchange of ideas. We look forward to seeing you at this minisymposium and engaging with you in discussion.
Experimentally Validating Model Predictions to Define Mechanisms of Respiratory Infections

Amber Smith*, St. Jude Children’s Research Hospital, amber.smith@stjude.org

Mathematical models of infection kinetics can quantify the rates of various processes, detail the time scales and mechanisms of pathogen control, identify novel mechanisms of host-pathogen interaction, assess efficacy of therapies, among others. However, limited data is often used to calibrate these models, which in turn reduces the mathematical and biological complexity that can be included and the questions that can be addressed. Nevertheless, accurate predictions are still possible, but knowledge of this accuracy (or inaccuracy) is unavailable unless follow-up experiments are completed. Here, I will use models of viral and viral-bacterial respiratory infections to illustrate how model-driven experiments can define additional biological mechanisms and highlight a model’s successes and failures. Finally, I will provide the foundation to further discuss the art of designing experiments, the integration of different types of data in immunological models, and the importance of understanding experimental details in model development and interpretation.
Tissue Damage as a Biomarker and Immune Stimulus in Inflammation Models

Judy Day*, University of Tennessee, judyday@utk.edu

This talk will briefly outline some of the work that inspired the use of a tissue damage variable in mathematical models of infectious and noninfectious inflammation as a marker for health as well as a driver of inflammation. Beginning with the setting of systemic inflammation in sepsis-related scenarios of infection, this overview will go on to discuss recent modeling work in the setting of non-infectious trauma such as transplantation. The purpose of this talk is to present some guiding principles that are applicable in other areas of interest to members of this subgroup; for instance, immune function in wound healing, traumatic brain injury, and autoimmune disease. In addition, another aim of this talk is to provide a foundation from which to use small group brainstorming sessions to discuss where these topics intersect other areas of research both with respect to common ground as well as different scales and techniques.
Discussion on the Future of Mathematics in Immunobiology and Infection

Amber Smith*, St. Jude Children’s Research Hospital, amber.smith@stjude.org
Judy Day*, University of Tennessee, judyday@utk.edu
Jessica Conway*, Pennsylvania State University, jmc90@psu.edu

Mathematical modeling is becoming heavily integrated into areas of Immunobiology and Infection. In addition, there has been a trend towards using more data-driven techniques, integrating different types of data, and validating model predictions experimentally. We invite you to join us in a round-table discussion within the contexts of modeling various aspects of immunobiology and infection and of integrating experimental and clinical data into these models in order to inform experimental design. We will also discuss education in terms of improving the knowledge and skill sets of students working in these areas, learning new skills to enhance one’s research area, and enhancing resource awareness. In conclusion, we will discuss the future activities of the Subgroup and solicit member input on the vision for this group. We invite you to think about the activities that can best benefit you and the field in terms of idea generation, network expansion, collaboration, and funding mechanisms. We hope that, together, our subgroup can become a powerful resource aimed at providing one another with relevant and current knowledge, feedback, connections, and camaraderie.
MS19: Mathematical Modeling of Honeybees

Title: Mathematical Modeling of Honeybees

Organizer: Vardayani Ratti

Summary: Honeybees play an outstanding role economically and ecologically. Since 2006 beekeepers worldwide have reported elevated rates of colony losses. Various causes (e.g. Varroa destructor, viruses, Nosema ceranae, and pesticide exposure) have been linked to these losses. 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.
Schedule:

- **Why do hives die? Using mathematics to understand the mechanism of honey bee colony collapse**
  M. R. Myerscough, D. Khoury, A. Barron
  10:30 - 11:00

- **A mathematical model for Nosemosis**
  H. Eberl, E. Guzman-Novoa, A. Petric
  11:00 - 11:30

- **Population Dynamics of Honeybees: linking parasites, diseases, and nutritional effects**
  Y. Kang, M. Rodriguez, K. Messan, R. Page, G. DeGrandi-Homan
  11:30 - 12:00

- **Bee++: A Model of Honey Bee, Pathogen, and Plant Interactions**
  M. Betti, J. LeClair, L.M. Wahl, M. Zamir
  12:00 - 12:30
Why do hives die? Using mathematics to understand the mechanism of honey bee colony collapse.

Mary R Myerscough*

*University of Sydney, Sydney, Australia marym@maths.usyd.edu.au

Honey bees are vital to the production of many foods which need to be pollinated by insects. Yet in many parts of the world honey bee colonies are in decline. A crucial contributor to hive well-being is the health, productivity and longevity of its foragers. When forager numbers are depleted due to stressors in the colony (such as disease or malnutrition) or in the environment (such as pesticides) there are significant effects. These include a reduction in the amount of food (nectar and pollen) that can be collected and a reduction of the colony’s capacity to raise brood (eggs, larvae and pupae) to produce new adult bees to replace lost or old bees.

We use a set of differential equation models to explore the effect on the hive of high forager death rates. We track the population of brood, hive bees (who work inside the hive) and foragers (who bring back food to the hive) and we track stored food. Using data from experimental research we devised functions that described the effect of the age that bees first become foragers on their success and lifespan as foragers. In particular we examine what happens when bees become foragers at a comparatively young age and how this can lead to a sudden rapid decline of adult bees and the death of the colony.
A mathematical model for Nosemosis

H. Eberl∗, E. Guzman-Novoa, A. Petric

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Nosema ceranae and Nosema apis are microsporidian parasites of the Western honeybee (Apis Mellifera) that cause nosemosis, a widely distributed honeybee disease. Nosema outbreaks are mainly observed in Spring when the bees engage in hive cleaning activities during which they ingest the spores. Based on the Khoury-Myerscough-Barron model for honeybee colonies that distinguishes between hive and forager bees we develop a nosemia model in which disease transmission by uptake of spores from the environment is the main transition route. The temporal dynamics of the disease requires a non-autonomous formulation of the model for which we assume periodic coefficient functions to mimick seasonal changes.
Population Dynamics of Honeybees: linking parasites, diseases, and nutritional effects

Y. Kang\(^1\), M. Rodriguez\(^2\), K. Messan\(^3\), R. Page\(^4\), G. DeGrandi-Hoffman\(^5\)

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Honeybees are both ecologically and economically important as they pollinate 80 percent of our flowering crops, which constitute one-third of everything we eat; and annually pollinate $14 billion worth of seeds and crops in the U.S. Unfortunately, Honeybees have been under serious pressure from a mystery problem: Colony Collapse Disorder (CCD), which is syndrome defined as a dead colony with no adult bees or dead bee bodies but with a live queen and usually honey and immature bees still present. The exact causes and the triggering factors for CCD have not been understood yet. Researchers have seen proposed several possible causes including certain agricultural pesticides, poor nutrition, pathogens, and the parasitic mites Varroa destructor, which are also vectors of viral diseases. In this talk, we will present a couple of our on-going honeybee modeling projects to demonstrate how the synergy effects of the parasitic mite Varroa destructor and the related virus infections, as well as foraging behavior and nutrient status (such as the level of Vitellogeninin (Vg) in hives) in honeybee affect population dynamics of honeybee and health of colony, which may contribute to CCD.
Bee++: A Model of Honey Bee, Pathogen, and Plant Interactions

M. Betti∗1, J. LeClair2, L.M. Wahl3, M. Zamir4

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Honey bees societies and their interactions with the local environment are complex to say the least. As honey bees are used both as livestock and as a primary pollinator for many plants, accurate predictive models have become indispensable to management and conservation efforts. We develop a model, Bee++, which can simulate the interactions between honey bees, parasites, and toxins in a spatially and temporally heterogeneous landscape. This model predicts optimal parameters that lead to a thriving ecosystem in which honey bee colonies provide pollination services for long-term, sustainable crop yield as well as key parameters in predicting colony collapse. Bee++ is designed as a functional framework for simulating a multitude of scenarios related to honey bee health and management.
Mathematical modeling is an emerging approach to understand social behavior and mental disorders. The underlying psychological and psychiatric processes in these areas are complex and consist of both biological and psychological components. Thus the data obtained in these areas can be both biological and psychological, and at both population and intra-individual levels. Therefore a combination of tools is necessary to tackle these problems and analyze the data. While traditional statistical methods can be effective tools for investigating the psychological and psychiatric processes, mathematical modeling is a complimentary method that allows for modeling of biological systems and analysis at the intra-individual level. In this minisymposium, we hope to bring together mathematicians, statisticians, and social scientists in an effort to facilitate collaboration, to reduce the language barrier between these different fields, and to further develop the field of mathematical psychology and psychiatry.

**Intended Audience:** Mathematicians and Psychologists
Schedule:

- *Dynamic modeling of problem drinkers undergoing behavioral treatment*
  Rebecca Everett
  10:30 - 10:50

- *Modeling the Risk Factors and Behaviors that lead to Problem Drinking at the Individual and Population Level*
  Judith Canner
  10:50 - 11:10

- *Modeling heterogeneous and nonstationary psychological processes*
  Peter Molenaar
  11:10 - 11:30

- *Using mathematical models of biological processes in genome-wide association studies of psychiatric disorder*
  Amy Cochran
  11:30 - 11:50

- *Insights into depression from mathematical modeling of volume transmission*
  Janet Best
  11:50 - 12:10
Dynamic modeling of problem drinkers undergoing behavioral treatment

Rebecca A. Everett*
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North Carolina State University, Raleigh, NC

We use dynamical systems modeling to help understand how selected intra-personal factors interact to form mechanisms of behavior change in a group of problem drinkers. Our modeling effort illustrates the iterative process of modeling using individuals’ clinical data. Due to lack of previous work in modeling behavior change in individual patients, we build a preliminary model relying on psychological understandings of the relationships among the variables. We refine the model and enhance our psychological understanding through the iterative modeling process. Our results suggest that this is a promising direction in research in alcohol use disorders.
Modeling the Risk Factors and Behaviors that lead to Problem Drinking at the Individual and Population Level

Judith Canner*
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California State University Monterey Bay

In order to make treatment accessible, psychologists are interested in developing outpatient treatment for problem drinkers who want to reduce, but not necessarily abstain from, alcohol consumption. While medication and cognitive behavioral therapy have been shown to be effective outpatient treatments on average, there are still many factors that may impact and individuals success in reducing their drinking. We will use structural equation modeling to identify the risk factors and dynamic relationships between drinking habits and everyday behaviors and events that may impact a patient's success in reducing drinking. We hope that our efforts will lead to models that can enhance clinical practice in the treatment of problem drinkers.
Modeling heterogeneous and nonstationary psychological processes

Peter C.M. Molenaar*
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State University of Pennsylvania

The implications of ergodic theory for psychological data analysis are put forward, showing under which conditions results obtained in analysis of inter-individual variation generalize to the level of intra-individual variation. For Gaussian processes the necessary and sufficient conditions are given by two criteria: stationarity of the processes concerned and homogeneity of dynamic models across replications. Because most data obtained in psychology will violate one or both of these criteria, alternative methods of data analysis will be presented which can accommodate such violations. These include dynamic model fitting of non-stationary processes and heterogeneous replicated time series analysis. Applications of these alternative methods to real data will be presented.
Using mathematical models of biological processes in genome-wide association studies of psychiatric disorders

Amy Cochran*
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University of Michigan

Genome-wide association studies have implicated a large number of genes in psychiatric disorders such as bipolar disorder and schizophrenia. These genes, however, are usually weakly-associated and involved in diverse biological processes, thereby obscuring mechanisms for how such disorders arise. To better elucidate mechanisms, disorders can be tested for association with a set of genes that represent a biological pathway. Even so, mechanisms can remain elusive if ultimately a specific biological function is important. We propose and analyze a statistical test to implicate biological functions in psychiatric disorders. Our approach relies on mathematical models of biological processes to predict how strongly genes contribute to a certain biological function. These predictions are used to assign weights to genes, which are then incorporated into a statistical test on genetic data. To demonstrate, we use this statistical test to explore the role of calcium signaling in bipolar disorder.
Insights into depression from mathematical modeling of volume transmission

Janet Best*
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The Ohio State University

Depression is a debilitating neuropsychiatric disorder afflicting millions. Antidepressants, which primarily target the serotonin system, are one of the most widely prescribed classes of medications in the USA. Serotonergic neurons participate in volume transmission, with neurons in the raphe nuclei sending their axons to other nuclei where serotonin is released into the extracellular space, modulating the activity of the electrophysiological circuitry in the projection region. I will present recent work modeling volume transmission in the serotonergic system in healthy and depressed mice, with and without antidepressants and the sometimes surprising insights that arise.
Mechanical forces are key contributors to intracellular organization and morphogenesis. Tissue engineering, the controlled construction of tissues -- cells and their extracellular matrix (ECM) environment -- is a promising avenue of future biomedical applications. To realize this possibility, the dynamic and mutually interdependent mechanical relationship between cells and tissue morphogenesis has to be understood. The interdependence between cell and tissue mechanics has been captured by a long series of mathematical models: particle, lattice, vertex and partial differential equation models. The ability to prescribe cell behavior favors "agent"-based simulations, while analytical studies utilized partial differential equation models. Recent developments in the field include close integration with experimental data, where cell deformations, forces can be quantified and manipulated and hence model predictions tested. In turn, the models also shed light to the underlying organizational principle of the tissues.
Schedule:

- **Study of the mechanical regulation of the robust mitotic rounding in epithelial tissues**
  Ali Nematbakhsha, Wenzhao Suna, Pavel A. Brodskiy, Aboutaleb Amiri, Cody Narciso, Zhiliang Xu, Jeremiah J. Zartman, Mark Alber*
  10:30 - 11:00

- **Cell contractility and plasticity driven tissue morphogenesis**
  Andras Czirok*, Dona Greta Isai
  11:00 - 11:30

- **Modelling of cell extrusion in an epithelial monolayer**
  Zoltan Neufeld*, Adrian Noppe
  11:30 - 12:00

- **Parameterizing a lattice-free model of a cell proliferation assay**
  Matthew Simpson
  12:00 - 12:30
Study of the mechanical regulation of the robust mitotic rounding in epithelial tissues

Mitotic rounding during cell division is critical for preventing daughter cells from inheriting an abnormal number of chromosomes, a condition that occurs frequently in cancer cells. Cells must significantly expand their apical area and transition from a polygonal to circular apical shape to achieve robust mitotic rounding in epithelial tissues, which is where most cancers initiate.

However, how cells mechanically regulate robust mitotic rounding within packed tissues is unknown. Mitotic rounding will be analyzed in this talk using a newly developed multi-scale subcellular element computational model that was extensively calibrated using experimental data. Novel biologically relevant features of the model include separate representations of the apical membrane and cytoplasm of the cell. Regression analysis of predictive model simulations revealed that mitotic area expansion was largely driven by regulation of cytoplasmic pressure. Surprisingly, mitotic shape roundness within physiological ranges was shown to be most sensitive to variation in cell-cell adhesivity and stiffness.
Andras Czirok*, Dona Greta Isai

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**Cell contractility and plasticity driven tissue morphogenesis**

Cell movements often involve cell-exerted mechanical forces and suitably controlled changes in cell adjacency. Based on empirical data, we developed a computational modeling framework to explore the mechanics of multicellular assemblies. Mechanically coupled adherent cells are represented as particles interconnected with elastic beams which can exert non-central forces and torques. A macroscopic elasto-plastic behavior is modeled by a stochastic process consisting of a connectivity change followed by a relaxation to mechanical equilibrium. Model particles can also act as simulation agents and actively modulate their connectivity according to specific rules. As an example, anisotropic link insertion and removal probabilities can give rise to local cell intercalation and large scale convergent extension movements. Cell extrusion from an epithelial layer involves mechanical torques, and can generate bending moments within a stratified (multi-layered) epithelium -- a process likely to shape the early embryonic heart field. The proposed stochastic simulation of cell activities yields fluctuating tissue movements which exhibit the same autocorrelation properties as empirical data from avian embryos.
Modelling of cell extrusion in an epithelial monolayer

Cell extrusion is a process by which cells are eliminated from an epithelial layer without disrupting its protective barrier role. This can happen as part of the normal turnover of cells in a tissue, or it may involve mutated cells facilitating the spread of cancer cells. We use computer simulations based on an extended three-dimensional Cellular Potts Model to investigate the effects of localised biomechanical changes in a layer of cells to determine the key factors that can induce extrusion of a modified cell. Our results suggest that reduced cell-cell adhesion and/or increased contractile tension around the cell cortex both promote extrusion in a cooperative manner, while the strength of adhesion of the neighbouring normal cells to the basal surface also plays an important role in the process. Using theoretical approximations we develop a simplified model to determine and analyse qualitatively the thresholds in the values of the cell parameters for the extrusion of the cell from the layer.
Matthew Simpson

Applied and Computational Mathematics, Queensland University of Technology, Brisbane, Australia.

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**Parameterizing a lattice-free model of a cell proliferation assay**

Cell proliferation assays are routinely used to study how a population of cells, initially distributed at low density on a two-dimensional substrate, eventually grows to form a dense monolayer of cells. These experiments are used to study a diverse set of biological problems including tissue engineering, and drug design for putative cancer treatments. In this presentation we will present a discrete lattice-free model of a cell proliferation assay that incorporates cell movement, cell proliferation and cell-to-cell crowding. To apply this model to mimic a set of experiments, we invoke a number of simplifying assumptions and then estimate the model parameters using approximate Bayesian computation. To provide confidence in our results we apply the same method to several identically prepared experimental data sets. This approach allows us to explore the sensitivity of our approach to parameter estimation.
MS22: Disease Modelling and Control

Minisymposium on Disease Modelling and Control

Organizers:
Alexandra Teslya, Centre for Disease Modelling (CDM), York University, Canada, alexa512@gmail.com
Jacques Bélair, Centre de Recherches Mathématiques (CRM), Université de Montréal, Canada, belair@crm.umontreal.ca

Summary:
A goal of all health researchers is to determine effective control strategies that can be provided to patients that will help them recover, or (when recovery is unachievable) manage their health conditions. Mathematical and statistical models are employed within these contexts so that the effects of current control strategies can be quantified, and so that optimal control strategies can be identified (given model assumptions and uncertainties). Recent developments of disease modeling have seen mathematical models being developed to address vaccination, drug therapy use, public health campaigns, and even online applications used to journal chronic condition experiences. This minisymposium aims to showcase recent modeling research of the Centre for Research Modelling (CDM) and the Centre de Recherches Mathématiques (CRM) trainees on a wide variety of topics on disease control that are of theoretical merit and are significant to patient outcomes. The topics include HIV transmission and progression, vector and host control, and chronic condition management. These topics will be of interest to mathematical modellers and health researchers alike. The minisymposium provides the participants and audience an opportunity to discuss emerging research topics and new areas for research collaboration in the fields of disease modelling and health.
Schedule:

- *Threshold policy to interrupt transmission of WNV to birds*
  Weike Zhou*, Yanni Xiao, Robert A. Cheke, Jane M. Heffernan
  10:30 - 11:00

- *Interesting bifurcation dynamics in the threshold-delay model of the HIV infection of infants through breastfeeding*
  Redouane Qesmi, Jane M. Heffernan, Alexandra Teslya*, Jianhong Wu
  11:00 - 11:30

- *The effects of adherence to protease inhibitors in HIV therapy*
  Lauren McKenzie*
  11:30 - 12:00

- *Modeling brain lentiviral infections during antiretroviral therapy in AIDS*
  Weston C. Roda*, Michael Y. Li, Michael Akinwumi, Eugene L. Asahchop, Benjamin B. Gelman, Kenneth W. Witwer, Christopher Power
  12:00 - 12:30
Title: Threshold policy to interrupt transmission of WNV to birds

Abstract

We propose two models of West Nile Virus (WNV) with discontinuous right-hand sides, concerning the control strategies of culling mosquitoes or birds under threshold policy. The control strategy is implemented once the number of infected mosquitoes or birds exceeds a threshold level. The long-term behavior of the proposed non-smooth system is investigated and it is shown that as the threshold value varies, model solutions ultimately converge to different equilibria including some novel steady states. The results indicate that a previously chosen level of infected birds or mosquitoes can be maintained when the threshold policy and other parameters are chosen properly, which provides a possible control strategy when an emergent infectious disease cannot be eradicated immediately.
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B. Interesting bifurcation dynamics in the threshold-delay model of the HIV infection of infants through breastfeeding

It is known that the breast milk of HIV infected women contains HIV. And therefore, while breastfeeding is a significant factor in optimization of nutrition and protection against numerous childhood infections, it can also contribute to HIV infection of infants. It is important to establish the threshold of breastfeeding duration, which can lead to an in-host HIV infection and, subsequently, an epidemic in a population. Authors extended a general threshold-delay model given by Qesmi et al. (2015). The model incorporated within host virus dynamics and presented the infection process as a series of exposures. The new model depicts an intrinsic virus growth rate as a function of the number of infected females in the population. This is especially relevant in populations where several women contribute to breastfeeding of an infant. The model is reduced to an equivalent state-dependent delay equation model, which is analyzed using stability and numerical bifurcation analysis. One of the most biologically important features of the model is a backward bifurcation, as the result of which a bi-stability between an endemic and the disease-free equilibrium is possible, when the basic reproductive ratio $R_0$ is less than one. Additionally, from the numerical simulations and bifurcation analysis, it is evident that the in-host dynamics parameters determine whether a backward bifurcation is possible.
Authors: Lauren McKenzie* and Robert Smith?
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Title: The Effects of Adherence to Protease Inhibitors in HIV Therapy

Abstract: The theoretical effects of adherence to protease inhibitors in HIV treatment are investigated. Impulsive differential equations are used to develop a mathematical model of protease inhibitor monotherapy. A drug concentration threshold that defines when drug resistance will emerge is determined. The following research questions are addressed: a) how many doses may be missed before resistance emerges? b) How many subsequent doses must be taken to return to pre-interruption drug levels? Estimates are provided for all protease inhibitors approved by the US Food and Drug Administration. Results may help form the basis of future clinical trials.
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B. Title And Abstract

Modeling brain lentiviral infections during antiretroviral therapy in AIDS

Understanding HIV-1 replication and latency in different reservoirs is an ongoing challenge in the care of patients with HIV/AIDS. A mathematical model was created to describe and predict the viral dynamics of HIV-1 and SIV infection within the brain during effective combination antiretroviral therapy (cART). The mathematical model was formulated based on the biology of lentiviral infection of brain macrophages and used to describe the dynamics of transmission and progression of lentivial infection in brain. Based on previous reports quantifying total viral DNA levels in brain from HIV-1 and SIV infections, estimates of integrated proviral DNA burden were made, which were used to calibrate the mathematical model predicting viral accrual in brain macrophages from primary infection. HIV-1 and SIV provirus burdens in the brain increase over time. A moderately efficacious antiretroviral therapy regimen could eradicate HIV-1 infection in the brain that was dependent on brain macrophage lifespan and the presence of neurological comorbidity.
MS23: Mathematical Modeling of the Eye in Health and Disease

MINISYMPOSIUM:
MATHEMATICAL MODELING OF THE EYE IN HEALTH AND DISEASE

Organizers:
Tracy L. Stepien, Department of Mathematics, University of Arizona, Tucson, AZ, USA, stepien@math.arizona.edu
Timothy W. Secomb, Department of Physiology, University of Arizona, Tucson, AZ, USA, secomb@u.arizona.edu

Summary

Millions of people around the world are affected by visual impairment and blindness, and many diseases such as glaucoma, cataracts, macular degeneration, and diabetes are main contributors to vision loss. Furthermore, alterations in the eye can signify cognitive damage in neurodegenerative disorders such as Alzheimer’s and Parkinson’s diseases. Since structural and functional vascular features in the eye can be observed and measured noninvasively, related diseases can then be monitored easily if disease characteristics are known. However, there is lack of understanding of the complex eye physiology and relations between blood flow, blood pressure, and vascular structure, for example, which hinders the interpretation of measured data. Mathematical modeling of the physiology of the eye has recently applied fluid dynamics, mass transport, biomechanics, stochasticity, population dynamics, and systems biology, among other methods, to incrementally become closer to achieving the inherently difficult goal of improving the prevention, detection, and management of eye-related diseases. This minisymposium will highlight mathematical models and biological properties of the eye in health and disease to give insight on advancing clinical care.
Mathematical Modeling of the Eye in Health and Disease

Wednesday, July 19, 3:30–6:00, City Creek Room

Schedule:

- **An overview of mathematical modeling of the eye**
  Tracy L. Stepien*, Timothy W. Secomb
  3:30 - 4:00

- **Stochastic photoreceptor patterning in fly and human retinas**
  Robert Johnston*
  4:00-4:30

- **Self-organization, planar polarity, and active foams: A fish eye’s view**
  David K. Lubensky*, Jeremy Hadidjoj Hayden Nunley, Mikiko Nagashima, Pamela A. Raymond
  4:30 - 5:00

- **A Multiscale Model of Retinal Microcirculation Integrating Blood Flow and Tissue Mechanics with Neural Signaling**
  Riccardo Sacco*, Aurelio Giancarlo Mauri, Giovanna Guidoboni, Brent A. Siesky, Alon Harris
  5:00 - 5:30
AN OVERVIEW OF MATHEMATICAL MODELING OF THE EYE

Tracy L. Stepien*, Department of Mathematics, University of Arizona, Tucson, AZ, USA, stepien@math.arizona.edu

Timothy W. Secomb, Department of Physiology, University of Arizona, Tucson, AZ, USA, secomb@u.arizona.edu

Abstract

The functioning of the eye depends on multiple complex biological and physical processes. Mathematical modeling allows quantitative description of the mechanisms at play and their interactions. This can lead to better understanding of visual function, providing a basis for improved methods to prevent and treat eye-related diseases. In embryonic development, eyes are formed from outgrowths of the brain, and by extension the retina is considered part of the central nervous system. Since the retina and eye can be observed and measured noninvasively, information can be obtained over time during health and disease, and analyzed statistically. We will give an overview of current mathematical modeling efforts in various aspects of development, health, and disease and discuss possible new directions for future study.
STOCHASTIC PHOTORECEPTOR PATTERNING IN FLY AND HUMAN RETINAS

Robert Johnston*, Department of Biology, Johns Hopkins University, Baltimore, MD, USA, robertjohnston@jhu.edu

Abstract

A central challenge in developmental neurobiology is to understand how the myriad types of neurons in the human nervous system are generated. Stochastic gene expression mechanisms are crucial to differentiate neuronal subtypes and expand function. During stochastic fate specification, individual neurons randomly choose between different fates, resulting in unique patterns but consistent proportions of cell types among genetically identical organisms. My lab studies the stochastic mechanisms that specify the color-detecting photoreceptors in the fly and human retina. Fruit flies have a well-characterized retina and an abundance of genetic tools that enable molecular analyses of gene regulatory mechanisms. To overcome the challenges associated with human studies, we have developed a human retinal organoid system that recapitulates retinal development and photoreceptor specification. With these systems, we are interrogating how DNA elements, trans factors, and chromatin architecture control random on/off gene expression. Our molecular approaches are complemented by quantitative genetics to determine how natural variation in the genome impacts gene expression and photoreceptor specification. Finally, we conduct behavioral and functional assays to measure differences in color perception when photoreceptor fates are altered. By studying highly divergent organisms from multiple angles, we aim to define the unifying principles underlying stochastic fate specification during nervous system development.
SELF-ORGANIZATION, PLANAR POLARITY, AND ACTIVE FOAMS: A FISH EYE’S VIEW

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Pamela A. Raymond, Department of Molecular, Cellular, and Developmental Biology, University of Michigan, Ann Arbor, MI, USA, praymond@umich.edu

Abstract

The orderly packing and precise arrangement of epithelial cells is essential to the functioning of many tissues, and refinement of this packing during development is a central theme in animal morphogenesis. The mechanisms that determine epithelial cell shape and position, however, remain incompletely understood. Here, I investigate these mechanisms in a striking example of planar order in a vertebrate epithelium: The periodic, almost crystalline distribution of cone photoreceptors in the adult teleost fish retina. Based on observations of the emergence of photoreceptor packing near the retinal margin, I propose a phenomenological mathematical model in which ordered columns of cells form as a result of coupling between planar cell polarity (PCP) and anisotropic tissue-scale mechanical stresses. This model correctly predicts a number of features of cell packing in mutant and regenerated retinas. It also suggests an intriguing role for cell extrusion from the epithelium in certain mutants. I will close with some new data and speculations on the appearance of topological defects in the photoreceptor lattice.
A MULTISCALE MODEL OF RETINAL MICROCIRCULATION INTEGRATING BLOOD FLOW AND TISSUE MECHANICS WITH NEURAL SIGNALING

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Brent A. Siesky, Department of Ophthalmology, Eugene and Marilyn Glick Eye Institute, Indiana University, Indianapolis, IN, USA, bsiesky@indiana.edu
Alon Harris, Department of Ophthalmology, Eugene and Marilyn Glick Eye Institute, Indiana University, Indianapolis, IN, USA, alharris@indiana.edu

Abstract

Several sight-threatening diseases are associated with impairment of blood flow regulation, which is the mechanism deputed to maintain proper tissue perfusion. Blood flow regulation is particularly important in the retina, where several mechanisms contribute to determine vessel diameter and blood flow, including feedback mechanisms due to metabolic controls and feedforward mechanisms due to neurovascular coupling. Understanding and quantifying the relative importance of these mechanisms in health and disease may help clinical research in devising new strategies to preserve vision in many patients. Here, we address this issue from a theoretical viewpoint and we propose a multiscale model of retinal microcirculation that integrates: (i) blood flow; (ii) chemical reaction and transport across the arterial wall; and (iii) neural signaling from glial cells surrounding the blood vessel. The model aims at predicting alterations in arterial diameters as a function of space, time, biomechanical parameters and biochemical signals. Numerical simulations suggest that feedforward glial synthesis plays an important role in retinal functional hyperaemia and that impaired nitric oxide synthesis may significantly affect vascular regulation. In particular, nitric oxide levels lower than baseline do not favor vasoconstriction and increase vasodilation, consistently with experimental data, whereas elevated nitric oxide levels result in a pathologically marked vasoconstriction.
MS24: From cell to tissues: multiscale mathematical approaches for cancer development

SMB 2017, 17-21 July 2017, University of Utah, Salt Lake City, Utah, USA

Mini-Symposium:
From cell to tissues: multiscale mathematical approaches for cancer development

Organiser: Dumitru Trucu (University of Dundee; email: trucu@maths.dundee.ac.uk)
Co-organiser: Raluca Eftimie (University of Dundee; email: reftimie@maths.dundee.ac.uk)

Understanding the complex mechanisms of growth and spread of cancer in the human body remains one of the greatest challenges of modern science. At the hearth of this challenge stays the natural multiscale character of cancer development, by which genetic and molecular intra-cellular processes (at subcellular-scale) are interconnected with complex signaling enabling local inter-cellular interactions (at cell-scale), which are further interlinked to the collective dynamics of cell population (at tissue-scale). This cascade of events is particularly illustrated during the cancer cell invasion into tissue, which is a complex process that plays a key role in the growth and spread of cancer, culminating in the metastatic spread.

One common aspect in the progression of all cancers is the secretion of proteolytic enzymes that degrade the surrounding tissue and the extracellular matrix (ECM), and support local cancer cell invasion. In conjunction with enzymatic activities, increased cancer cell motility due to changes in cell-adhesion properties (via dynamically formed adhesion junctions and cell-surface binding from ECM ligands) further exacerbates the invasion. The cell-scale activities are however in a dynamic cross-talk with critical tissue-scale processes reflected in the evolving morphology and migration patterns of the cancer cell population.

To address these challenges, this mini-symposium explores the following important modeling and analysis aspects in cancer spread and development: (a) geometric PDE approaches for whole cell tracking; (b) evolutionary and ecological approaches in tumour progression; (c) nonlocal interactions of heterogeneous cancer cell population in invasion; (d) hybrid approaches in glioblastoma progression; and (e) multi-scale moving boundary modeling of cell-cell adhesion and matrix degrading enzymes dynamics in cancer invasion.

Speakers and Schedule (talks duration: 25 min talks +5 min questions):
1. Yangjin Kim (Konkuk University, South Korea)
2. Anotida Madzvamuse (University of Sussex, UK)
3. Tommaso Lorenzi (University of St Andrews, UK)
4. Vasiliki Bitsouni (University of Dundee, UK)
5. Dumitru Trucu (University of Dundee, UK)
Schedule:

- *Mathematical modeling of tumor growth: hybrid approaches*
  Yangjin Kim
  3:30 - 4:00

- *A novel approach for whole cell tracking based on geometric partial differential equations*
  Anotida Madzvamuse
  4:00 - 4:30

- *A partial differential equation approach to studying evolution in cancer cell populations*
  Tommaso Lorenzi
  4:30 - 5:00

- *Dynamics in a nonlocal heterogeneous population model of cancer cell growth and invasion*
  Vasiliki Bitsouni, Raluca Eftimie
  5:00 - 5:30

- *Multiscale modelling of cancer growth and spread*
  Dumitru Trucu
  5:30 - 6:00
SMB 2017, 17-21 July 2017, University of Utah, Salt Lake City, UT, USA
Mini-Symposium: *From cell to tissues: multiscale mathematical approaches for cancer development*. Organizers: Dumitru Trucu and Raluca Eftimie

**Author:**
Yangjin Kim*
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**Title:**
*Mathematical modeling of tumor growth: hybrid approaches*

**Abstract:**
Glioblastoma (GBM) is one of the most lethal type of brain cancer with poor survival time. GBM is characterized by infiltration of the cancer cells through the brain tissue while lower grade gliomas and other non-neural metastatic types form self-contained non-invasive lesions. GBMs are highly invasive and difficult to treat because cells migrate into surrounding healthy brain tissue rapidly, and thus these tumors are difficult to completely remove surgically. We develop various mathematical models to investigate the basic mechanisms of glioma infiltration through the extracellular matrix and other cells in the absence and presence of blood vessels. The hybrid method allows us to investigate the multi-scale (space and time) nature of tumor progression in GBM and other cancers including breast cancer. We develop a multi-scale hybrid model where inter- and intracellular signaling network in response to diffusible macroscale factors (PDEs) controls the behavior of lattice-free individual cancer cells. In the presence and absence of extracellular matrix (ECM) and blood vessels, the behavior of tumor cells adapt to the system, resulting in resistant cancer cells. We show that the model’s predictions agree with experimental results for a glioma. We also develop new therapeutic strategies to eradicate the infiltrative glioma cells via the miR-451-AMPK-mTOR-cell cycle signaling network. We present EMT process via RAF-MEK-ERK-RKIP-SLUG-SNAIL-ZEB1 dynamics. The dynamical system of this signaling network within the invasive glioma cells and EGF-TGFbeta dual bifurcations with bi-stability suggests several hypotheses on new therapeutic anti-invasion strategies and new experiments as a test bed.
SMB 2017, 17-21 July 2017, University of Utah, Salt Lake City, UT, USA
Mini-Symposium: From cell to tissues: multiscale mathematical approaches for cancer development. Organizers: Dumitru Trucu and Raluca Eftimie

Author:
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Department of Mathematics, School of Mathematical and Physical Sciences, University of Sussex, Brighton, BN1 9QH, UK
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Title:
A novel approach for whole cell tracking based on geometric partial differential equations

Abstract:
In this talk, I will present a novel approach for whole cell tracking based on geometric partial differential equations for the cell surface motion where the physics of the migrating cell is easily encoded. In order to fit to experimental data an optimal control framework using phase-field theory is presented. A highly efficient, adaptive and fast multigrid solver is then employed to allow for realistic 2D and 3D simulations. Numerical examples will be exhibited that show the applicability of the mathematical framework for whole cell migration. Cell migration is a multistep process essential for mammalian organisms and is closely linked to processes such as development, immune response, wound healing, tissue differentiation and regeneration, inflammation, tumour invasion and metastasis formation.
A partial differential equation approach to studying evolution in cancer cell populations

Abstract:
A growing body of evidence supports the idea that solid tumours are complex ecosystems populated by cells with heterogeneous phenotypes, whose dynamics can be described in terms of evolutionary and ecological principles. Under this perspective, it has become increasingly recognised that mathematical modelling can complement experimental cancer research by offering alternative means of interpreting experimental data and by enabling extrapolation beyond empirical observation. This talk deals with mathematical models formulated in terms of partial differential equations which can be used to study the evolutionary dynamics of cancer cell populations. In particular, I will present a number of results which illustrate how analysis and numerical simulation of these equations can help to uncover fresh insights into the critical mechanisms underpinning tumour progression and the emergence of resistance to cytotoxic therapy.
SMB 2017, 17-21 July 2017, University of Utah, Salt Lake City, UT, USA
Mini-Symposium: From cell to tissues: multiscale mathematical approaches for cancer development. Organizers: Dumitru Trucu and Raluca Eftimie

Authors:
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Title:
Dynamics in a nonlocal heterogeneous population model of cancer cell growth and invasion

Abstract:
Cells adhere to each other and to the extracellular matrix (ECM) through protein molecules on the surface of the cells. The breaking and forming of adhesive bonds, a process critical in cancer invasion and metastasis, can be influenced by the mutation of cancer cells. We present a model of nonlocal partial differential equations coupled with ordinary differential equations, describing cancer cell invasion and movement as a result of integrin-controlled cell-cell adhesion and cell-matrix adhesion, for two cancer cell populations with different levels of mutation. We use this model to investigate the role of cancer mutation on the possibility of cancer clonal competition with alternating dominance, or even competitive exclusion. We discuss different possible cell aggregation patterns, as well as travelling wave patterns, and we investigate the effect of cancer mutation rate on the speed of cancer invasion.
Recognized as one of the hallmarks of cancer, cancer cell invasion into tissue is a complex process that plays a key role in the growth and spread of cancer, culminating in metastatic spread (secondary cancers). One common aspect of all cancer progression is the secretion of matrix degrading enzymes (MDEs) by the cancer cells that modify or destroy the surrounding tissue or extracellular matrix (ECM) and support local cancer cell invasion. In conjunction with MDE activities, increased cancer cell motility due to changes in cell-adhesion properties further exacerbates the invasion. Transmembrane calcium-dependent adhesion molecules (cadherins) interact with intra-cellular proteins, such as β-catenin and give rise to adhesion junctions. Of particular importance in cancer invasion are the dynamics between the calcium-sensing receptor distribution and the calcium ions (Ca2+) from the ECM. In addition to cell-cell adhesion, the binding of various ECM ligands to cell-surface receptors (integrins) enables cell-matrix adhesion. Thus, processes occurring at a molecular (micro) scale give rise to processes occurring at the tissue (macro) scale, via processes taking place at the cellular (meso) scale. The interplay between micro-, meso- and macro-scale processes involved in cancer cell invasion are still not fully understood. This talk will address recent advancements in multiscale modelling of cell-cell adhesion inside the tumour in conjunction with the activity of various proteolytic processes occurring along the invasive edge of the tumour. Finally, we will present computational simulations of the resulting multiscale moving boundary model and discuss a number of important fundamental properties that follow.
What is the historical context of education at the interface between the mathematical and biological sciences? What is current and exciting in that area now? What needs to be done? What challenges do we face? In this minisymposium we want to initiate civil discourse about the roles we play as educators in mathematical biology. We will share ideas about improving the teaching and learning of topics in mathematical biology and undergraduate research. We will discuss challenges we face now and we will look toward the horizon and think about what will come next. We hope to inspire and motivate those in attendance to reflect on what can be done to promote mathematical biology education and encourage further meaningful developments and to turn it into action.
Schedule:

- *From Slide rules, Calculators, Computers, to eScience in Support of Developing Mathematical Reasoning: Four Generations of Mathematica Education Technology and Education*
  John R. Jungck
  3:30 - 4:00

- *An Undergraduate Course in Mathematical Epidemiology*
  Meredith L. Greer
  4:00 - 4:30

- *REU for Training in the Use of High Performance Computing: Mathematical Biology Applications*
  Brad Peercy
  4:30 - 5:00

- *The Leaky Pipeline for Women in STEM: Global Challenges*
  Elissa J. Schwartz*, Rejoyce Gavhi-Molefe
  5:00 - 5:30

- *MathWorks and the Society for Mathematical Biology*
  Fulden Buyukozturk
  5:30 - 6:00
From Slide rules, Calculators, Computers, to eScience in Support of Developing Mathematical Reasoning: Four Generations of Mathematical Biology Education Technology and Education

John R. Jungck

University of Delaware, jungck@udel.edu

Learning in Mathematical Biology classrooms and laboratories has gone through four generations since Sputnik and the STEM education reform initiatives that responded to that international challenge. In a very conservative analysis by a skeptic of reform, Richard Askey (1999) characterized three revolutions as “New Math,” “Back-to-Basics,” and “NCTM standards” and foreshadowed an impending fourth movement which we might now recognize as “Common Core” or “Next Generation Science Standards.” In 2000, Lynn Steen responded with a series of questions that presented a very different perspective on the issues that respected educational and cognitive science research. Changes in the technology deployed are obvious benchmarks that we have had to respond to over this time frame of the past sixty years. However, there are at least three other drivers that correspond to, but are sometimes uncoupled from these changes, that address the context and goals of mathematics education. First, the focus of what mathematics is important to biologists has simultaneously changed from a primary focus on theorems, proofs, and problems in calculus to the inclusion of modeling, statistics, linear algebra, combinatorics, and even some computational thinking. Second, the movement away from proprietary interests towards open science, open source, Creative Commons, copyleft, crowdsourcing, and Citizen Science has fundamentally changed the resources that we have available as well as the potential for students engaging in work for the common good, participatory democracy, and active responsible citizenship. These efforts have often called upon the historical contributions to mathematics in the growing field of ethnomathematics and the challenges and opportunities to address issues of social justice, equity, and inclusion. Third, our pedagogy has similarly changed from “sages on stages” to “guides on the sides” to “meddlers in the middle” as we shifted from instructionalist pedagogies designed to “sort and select” students to learner-centered classrooms designed to improve retention and graduation rates, especially of historically underrepresented groups.
Mathematical Epidemiology can be the perfect elective-level course for an undergraduate. Background need not include more than some calculus and linear algebra. Students start on Day 1 by delving into the scope of what mathematics can accomplish, as well as beginning to build basic models of disease spread. Content throughout the semester includes differential equations, linear algebra, use of data, reading the literature, synthesizing ideas, writing about process and results, and incorporating current events. The topics in this course strengthen and expand upon the mathematical background students learned in earlier studies. This talk discusses semester-long structure, ideas for writing assignments, using epidemiological applications to improve student understanding of mathematical theory, and balancing prepared semester materials with impromptu discussion of current events.
REU for Training in the Use of High Performance Computing: Mathematical Biology Applications

Brad Peercy
University of Maryland-Baltimore County, bpeercy@umbc.edu

Over the last 7 years at UMBC we have run an REU site funded by NSF, NSA, and UMBC’s Meyerhoff program that teaches the basics of parallel computing on a state of the art cluster. As one of the largest REU sites we bring in 24-33 broadly diverse students each year and form teams of 4-5 students. Clients present computationally intensive problems to the teams who then propose solutions. Several of these projects address biological phenomena such as clustering of beta cells in a computational islet, probabilistic release of calcium in a cardiac cell, and most recently clustered cell migration in a drosophila egg chamber. We will discuss the training component, the evolution of the client selection process, and highlight several results many of which have led to student publications.
The Leaky Pipeline for Women in STEM: Global Challenges

Elissa J. Schwartz\textsuperscript{1,*} and Rejoyce Gavhi-Molefe\textsuperscript{2}

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*presenting speaker

The success of mathematical biology education initiatives relies upon the retention of students in STEM disciplines. More efforts are needed to improve retention rates in STEM, especially of historically underrepresented groups. Not only are women and underrepresented groups important components of the workforce, but STEM fields can benefit from the wider range of solutions contributed by diversity in its researchers. Progressing on the path towards STEM careers is not always easy, however, and many young women disappear along the way. This loss of women is a common phenomenon in academic systems around the globe and has been described as the “leaky pipeline.” The leaky pipeline for women in STEM careers starts at early stages, continues throughout the career trajectory, and gradually results in a small proportion of women researchers.

We initiated a pilot study to begin to remedy the situation, focusing on Africa. Following a group discussion in which participants from 15+ countries in Africa identified ‘mentoring’ as a potential solution to the leaky pipeline for women in STEM in their communities, we created a program for professional development, mentoring, and support for one particular group, female African students in the one-year coursework master’s program in mathematics at the African Institute of Mathematical Sciences (AIMS) – South Africa. Through the pre-existing AIMS Women in STEM (WIS) Mentoring/Outreach Initiative, we held mentoring sessions, mentoring lunches, and began a mentor-mentee matching program.

Mentoring sessions included presentations on the career journeys of women researchers in STEM, including the challenges they faced and obstacles they overcame, and panel discussions on professional development. The one-on-one mentoring program matched 13 mentor-mentee pairs. Pairs met once per week for 4 weeks, with the option for a second pairing in an additional 4-week session. Mentors and mentees could focus on any or all of three aspects: navigating the career path, choosing a research area in mathematics, and discussion of personal challenges encountered. Thirdly, we arranged mentoring lunches for the informal discussion of career development, related issues, and mutual support.

Exit survey feedback from the three initiatives we implemented will be presented, focusing on whether these programs increased or decreased the students’ perception of their available resources to succeed, other benefits reported, and what role these programs may play to increase the likelihood that the women continue in STEM careers. This talk will conclude with an audience discussion regarding what may best address this issue of retention in STEM and related topics.
Teaching Modeling and Simulation using MATLAB: Case Studies in Systems Biology and Pharmacology

Fulden Buyukozturk\textsuperscript{1}, Jerry Brusher\textsuperscript{1}, Santiago Schnell\textsuperscript{2}, Jagesh Shah\textsuperscript{3}

\textsuperscript{1} MathWorks, Natick, MA
\textsuperscript{2} University of Michigan Medical School, Ann Arbor, MI
\textsuperscript{3} Harvard Medical School, Boston, MA

Modeling and simulation (M&S) is an integral part of both Systems Biology and Pharmacology education. The dynamical mechanisms of living systems can be difficult to reveal in a laboratory setting; however, through a combination of laboratory measurements and mechanistic model building, M&S approaches can provide a substrate for hypothesis testing. In addition, increased adoption by the Pharmaceutical Industry of model-based approaches to the development of new therapies intensifies the demand for strong M&S skills in graduating students. Here, we present two case studies that address the need to incorporate computational M&S into the biological sciences curriculum.

First, we consider \textit{Computational Systems Biology}, offered to Physiology and Bioinformatics graduate students at the University of Michigan. The goal of this course is to enable students to translate descriptions of biological and physiological processes into mathematical models, which can then be solved numerically using MATLAB. This course serves students with a variety of undergraduate backgrounds and programming experience, and therefore utilizes online training resources and a summer workshop to establish basic computational skills. By level-setting students in advance, the course can focus on the domain-specific application of M&S rather than on generic training on the tools. We found that graphical-based tools with a block diagram for modeling are helpful to introduce dynamical systems/ODE modeling to biomedical scientists with no advance calculus or programming experience.

Secondly, we examine \textit{Quantitative Methods in Pharmacology} for graduate students at Harvard Medical School. The course focuses on computational pharmacology and follows a flipped classroom approach: students review the background material outside of class and spend class time working hands-on with SimBiology. SimBiology is a MATLAB-based tool that offers both an intuitive graphical approach and a programmatic interface to modeling biological systems. It also includes functions and capabilities to perform common tasks, such as simulation to predict system behavior, sensitivity analysis to identify significant biological pathways, and parameter estimation to fit models to data. By using SimBiology, students quickly and easily implement and analyze models of complex biological and pharmacological processes. To help students appreciate the relevance of the content, the course invites guest lecturers from industry to speak about the use of SimBiology, systems approaches, and M&S in pharmaceutical research. One iteration of the course had the students generate a model related to their thesis research, permitting them to recast their work in a quantitative modeling framework for M&S. The course evaluations have been uniformly positive, with many of the students noting that the skills and concepts they acquired were immediately applicable to their research projects.
Overexploitation of our natural resources is the greatest driver of biodiversity loss around the globe. A large portion of this exploitation is illegal. In this symposium we explore the interface between mathematical biology and criminology with the aim to create a healthier planet by reducing crime (in its own right) and its impact on fragile biological and social systems. In order to reduce criminal activity, we must understand the emergent patterns resulting from dynamic models of crime and how it responds to enforcement. Mathematical analysis and simulation should play a central role in the future of criminology, as theoretical studies of how crime responds to different management interventions can prevent unintended perverse outcomes of new policies before deployment. In this symposium, we show how traditional models from epidemiology, ecology and bio-economics can be used to understand crime, and explore the effect of different management approaches on reducing illegal activity and its effect on the environment. Finally we describe an emerging field of computer science called “green security games,” which offers novel solutions.
Schedule:

- **The Dynamics of Illegal Harvest: How to Save the African Elephant from Poaching**
  Matthew H. Holden*, Duan Biggs, Henry Brink, Hugh Possingham, Jonathan Rhodes Eve McDonald-Madden
  3:30 - 3:55

- **A model for rioting activity: shocks, diffusion, and thresholds**
  Nancy Rodriguez*
  3:55 - 4:20

- **Mathematical Modeling of Criminal Behavior**
  Joanna Sooknanan*, Donna M. G. Comissiong
  4:20 - 4:45

- **Radicalization within Sectarian Conflict**
  Maria R D’Orsogna*, Yaoli Chuang, Tom Chou
  4:45 - 5:10

- **An Introduction to Green Security Games with Applications to Illegal Logging**
  Sara Mc Carthy*, Milind Tambe, Christopher Kiekintveld, Meredith L. Gore, Alex Killion
  5:10 - 5:35

- **Adversary Behavior Modeling and Forecasting with Real-World Poaching Data**
  Debarun Kar, Benjamin Ford*, Shahrzad Gholami, Milind Tambe, Fei Fang, Andrew Plumptre, Margaret Drinciu, Aggrey Rwetsiba, Mustapha Nsubaga, Joshua Mabonga
  5:35 - 6:00
Matthew H. Holden*, University of Queensland, Australia, m.holden1@uq.edu.au

Duan Biggs, University of Queensland, Australia, d.biggs@uq.edu.au

Henry Brink, Northern Territory Government Department of Environment and Natural Resources, Australia

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Hugh Possingham, University of Queensland, Australia, h.possingham@uq.edu.au

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Eve McDonald-Madden, University of Queensland, Australia, e.mcdonaldmadden@uq.edu.au

The Dynamics of Illegal Harvest: How to Save the African Elephant from Poaching

Complex dynamics can arise from simple differential equations that couple economic market and wildlife population processes. Subtle changes in model structure can be the difference between stable, abundant populations and extinction. After briefly discussing the theory of open-access harvest models and their implication for conservation, we will examine the projected trajectories of African elephant populations threatened by poaching for ivory. The three most commonly proposed solutions to prevent population declines are to 1) increase anti-poaching enforcement effort, 2) reduce consumer demand for ivory or 3) legalize and regulate ivory trade, to flood the market with ivory, decreasing price and therefore the incentive to poach, and in addition generate revenue to fund elephant conservation. Analyzing a simple model of elephant population dynamics and ivory demand, we find that even with assumptions that favor the effectiveness of all three strategies, none are likely to lead to equilibrium population sizes at or above current population levels, without achieving formidable targets. For example, we find that demand reduction efforts must reduce price by 79-90%, to prevent population declines. Legalized trade requires an unsustainable supply of ivory, even if revenue funds anti-poaching enforcement, unless demand is completely insensitive to price. Quickly adopting innovative methods to curb poaching is a necessity for achieving the formidable targets required to sustain current elephant population sizes.
Nancy Rodriguez*, University of North Carolina at Chapel Hill, nrod@unc.edu

A model for rioting activity: shocks, diffusion, and thresholds

In this talk I discuss a reaction-diffusion system describing social outbursts of activity, such as rioting. The system can be used to represent a general type of phenomena in which one variable exhibits self-excitement once the other variable has reached a critical value. There are two regimes of interest that lead to either monotone or nonmonotone traveling waves. After explaining the theory, I will discuss what modeling can tell us about the 2005 French riots that lasted approximately 45 days and spread throughout the country.
Joanna Sooknanan*, University of Trinidad and Tobago,

Donna M. G. Comissiong, The University of the West Indies,
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Mathematical Modeling of Criminal Behavior

Mathematical models offer crucial insights into the transmission dynamics and control of infectious diseases. These infectious disease models have also been applied to investigate a variety of ‘contagious’ social phenomena like addiction, fanaticism and criminal behavior. Models can be used to generate estimates where data is sparse, examine possible “what if” scenarios and allow for the evaluation of mitigation schemes. In this talk, we examine a mathematical model in which criminal gang membership is treated as an infection (motivated by peer pressure) that spreads through a community by interactions among gang members and the population.
Radicalization within Sectarian Conflict

We introduce a two-variable lattice model to describe conflict within communities. Individuals may harbor a continuous belief variable and a discrete radicalization level. We also include a bistable radicalization process that models memory-dependent social behavior, and institutional influence, such as propaganda or education. In some parameter regimes, we find that institutional influence may suppress radicalization and allow for social conformity and appeasement over time. In other cases, institutional intervention may be counterproductive and exacerbate the spread of radicalization within a non-homogeneous population.
Sara Mc Carthy*, University of Southern California, sara.m.mccarthy@gmail.com,

Milind Tambe, University of Southern California, tambe@usc.edu,

Christopher Kiekintveld, University of Texas, El Paso,

Meredith L. Gore, Michigan State University, gorem@msu.edu,

Alex Killion, Michigan State University

An Introduction to Green Security Games with Applications to Illegal Logging

Green Security Games refers to the general framework to model the repeated and strategic interaction between defenders and adversaries in environmental security domains such as wildlife and fishery protection. Conservation agencies, tasked with defending large conservation areas and reserves, are often faced with the challenge of limited budgets and resources for protecting these areas, making it crucial to allocate these resources efficiently. We show how game theory can be used for strategic decision support at the management level to analyze long term investments in security resources and determine the best way to build a team of patrollers with a limited budget, as well as tactical decision support, optimizing over the deployment of these resources, and create patrols that account for many different variables (e.g., limited patrol units to send out, multiple locations that poachers can attack at varying distances to the outpost) in order to protect these areas. We look specifically at the challenge of optimizing the defense of forests against illegal logging, and provide scalable algorithms solve this problem, evaluating our methods on a variety of synthetic examples, as well as a real-world case study using data from our on-going collaboration in Madagascar.
Poaching is a serious threat to the conservation of key species and whole ecosystems. Park rangers are responsible for protecting wildlife from poachers, most commonly via foot patrols. Given that rangers must patrol vast areas with limited patrolling resources, adversary behavior modeling and prescriptive analytics can aid rangers in patrolling and protecting species more effectively. In this work, we introduce the Protection Assistant for Wildlife Security (PAWS) and its predictive and prescriptive analytics components. We discuss recent PAWS efforts to (i) model poacher behavior using graphical models and decision tree ensembles, (ii) evaluate modeling efforts with 12 years of real-world patrolling data from Uganda’s Queen Elizabeth National Park (QENP), and (iii) field test predictive models in QENP - a first for adversary behavior modeling applications in this domain.
Agent-based modeling as a tool to study complex multi-scale biological systems

MINISIMPOSIUM SUBMISSION – SMB 2017 - July 17-20, 2017, University of Utah, Salt Lake City

Organizer: Simeone Marino

Co-organizer: Denise E. Kirschner

Title: Agent-based modeling as a tool to study complex multi-scale biological systems

Summary: There is a great need in systems biology to integrate data across multiple time and length scales in order to mimic the complexity of real life phenomena. Mathematical and computational models can be used to integrate these different types of data, as well as to bridge between experimental measurements, better understand hypothesized mechanisms, run virtual experiments (e.g. virtual clinical trials, virtual deletions/depletions) when animal experiments are too expensive or difficult, interpret data, and offer new explanations for observed phenomena.

Agent Based Models (ABMs) are one of the tools emerging as more adequate to represent phenomena in a more familiar way to biologists and experimentalists, without limiting the mathematical and computational assumptions.

This minisymposium will offer several examples of ABMs applied to infectious disease, microbiology, cancer and more. Challenges encountered in analyzing and interpreting the results will also be discussed (e.g., uncertainty and sensitivity analysis).

Intended Audience: Graduate, PhD students, PostDoctoral fellows, and Faculty interested in applying stochastic and multiscale models such as Agent-Based Models to their research. A wide variety of applications in biology are presented.

Speakers and affiliations

1) Gary An, The University of Chicago Medicine, email: gan@surgery.bsd.uchicago.edu Title: High performance computing-augmented use and analysis of agent-based models: pathways to new math for biology

2) Kenneth Blahut, Department of Physics, Ryerson University, E-mail: kblahut@ryerson.ca Title: Quantifying free virus and cell-to-cell infection of HCV using an agent-based model.

3) Vittorio Cristini, PhD – Rochelle and Max Levit Chair in the Neurosciences, University of Texas System STAR Fellow, Adjunct Professor of Imaging Physics, MD Anderson Cancer Center, Professor with tenure and Director Center for Precision Biomedicine | Institute for Molecular Medicine, email: vittorio.cristini@uth.tmc.edu, _Title/Abstract: Mechanistic patient-specific predictive correlation of tumor drug response with microenvironment and perfusion measurements

4) Hayley Warsinske PhD Khatri Laboratory Stanford University, email: warsinhc@stanford.edu Title: Agent based model reveals dichotomous regulation of immune cells by TGF-β1 and IL10 in a Tuberculosis Granuloma

5) Kerri-Ann Norton, Systems Biology Laboratory, Department of Biomedical Engineering, School of Medicine Johns Hopkins University, email: knorton4@jhmi.edu Title: A Multiscale Agent-Based Model of Triple-Negative Breast Cancer Stromal Heterogeneity: Contributions of Tumor Associated Macrophages and Cancer Associated Fibroblasts
Agent-based modeling as a tool to study complex multi-scale biological systems

Schedule:

- High performance computing-augmented use and analysis of agent-based models: pathways to new math for biology
  Gary An
  3:30 - 3:55

- Quantifying free virus and cell-to-cell infection of HCV using an agent-based model
  Kenneth Blahut
  3:55 - 4:20

- Mechanistic patient-specific predictive correlation of tumor drug response with microenvironment and perfusion measurements
  Vittorio Cristini
  4:20 - 4:45

- Agent based model reveals dichotomous regulation of immune cells by TGF-β1 and IL10 in a Tuberculosis Granuloma
  Hayley Warsinske
  4:45 - 5:10

- Multiscale Agent-Based Model of Triple-Negative Breast Cancer Stromal Heterogeneity: Contributions of Tumor Associated Macrophages and Cancer Associated Fibroblasts
  Kerri-Ann Norton
  5:10 - 5:35
HPC-augmented use and analysis of agent-based models: pathways to new math for biology

Gary An, MD
Professor of Surgery
University of Chicago
docgca@gmail.com

Agent-based models (ABM) are an increasingly popular means of representing biological systems, most often as aggregations of different types of cells. The benefit of agent-based models (ABMs) is that they represent an intuitive way for bioscientists to translate their mechanistic knowledge into computational form. However, ABMs lack a unifying mathematically formal description, causing them to be treated mostly as in silico experimental objects, with limitations similar to that of biological experimental models. They are additionally hampered by being held to the same rigorous validation criteria as simulations from the physical sciences (which emphasize precision of prediction). The key difference here is that the physical sciences are governed and constrained by known natural laws, while biology is not (except for evolution). Therefore, existing approaches to evaluating and using computer simulation/mathematical modeling may not be suited to their investigation of biology. This talk will present the argument that the key to biology is its ability to generate heterogeneity at the system level from a shared, common functional structure, manifesting as biological objects' existence as parameter spaces of conserved functional forms, and that high-performance computing (HPC) implementations of ABMs can be used as proxy systems to generate simulated data at sufficient scale to approximate those behavioral topologies. This concept of biological systems and the associated use of computational proxy models offers the promise of addressing several major challenges facing bioscience today: 1) The Crisis of Reproducibility, where experimental and clinical studies cannot be replicated, 2) the Translational Dilemma, which is the gap between knowledge generated at the bench and its implementation in effective clinical therapeutics, 3) and Precision Medicine, which should mean the right drug for the right patient at the right time, but is hampered by poor characterization of pathophysiological dynamics.
Quantifying free virus and cell-to-cell infection of HCV using an agent-based model.

Kenneth Blahut$^{1,*}$, Jordan J. Feld$^{2,3}$, Shingo Iwami$^4$, and Catherine A.A. Beauchemin$^1$

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$^2$Toronto Centre for Liver Disease, University of Toronto, Toronto, Canada
$^3$Toronto Western Hospital Liver Center, Toronto, Canada
$^4$Department of Biology, Kyushu University, Fukuoka, Japan

March 8, 2017

Abstract

Experiments have shown that hepatitis C virus (HCV) infections in vitro disseminate both distally via the release and diffusion of cell-free virus through the medium, and locally via direct, cell-to-cell transmission. To determine the relative contribution of each mode of infection to HCV dissemination, we developed an agent-based model (ABM) that explicitly incorporates both distal and local modes of infection. The ABM tracks the concentration of extracellular infectious virus in the supernatant and the number of intracellular HCV RNA segments within each infected cell over the course of simulated in vitro HCV infections. Experimental data for in vitro HCV infections conducted in the presence and absence of free-virus neutralizing antibodies was used to validate the ABM and constrain the value of its parameters. We found that direct, cell-to-cell infection accounts for 96% of infection events, making it the dominant mode of HCV dissemination in vitro. Yet, when infection via the free-virus route is blocked, a 60% reduction in the number of infection events at 72 hpi is observed experimentally; a result that is reproduced by our ABM. Taken together, these findings suggest that while HCV spread via cell-free virus contributes little to the total number of infection events in vitro, it plays a critical role in enhancing cell-to-cell HCV dissemination by providing access to distant, uninfected areas, away from the already established large infection foci.
Agent-based modeling as a tool to study complex multi-scale biological systems

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www.uth.edu/imm/centers/center-for-precision-biomedicine.htm

TITLE
Mechanistic patient-specific predictive correlation of tumor drug response with microenvironment and perfusion measurements

ABSTRACT
Physical properties of the microenvironment influence penetration of drugs into tumors. Here, we develop a mathematical model to predict the outcome of chemotherapy based on the physical laws of diffusion. The most important parameters in the model are the volume fraction occupied by tumor blood vessels and their average diameter. Drug delivery to cells, and kill thereof, are mediated by these microenvironmental properties and affected by the diffusion penetration distance after extravasation. To calculate parameter values we fit the model to histopathology measurements of the fraction of tumor killed after chemotherapy in human patients with colorectal cancer metastatic to liver (coefficient of determination $R^2 = 0.94$). To validate the model in a different tumor type, we input patient-specific model parameter values from glioblastoma; the model successfully predicts extent of tumor kill after chemotherapy ($R^2 = 0.70.91$). Toward prospective clinical translation, we calculate blood volume fraction parameter values from in vivo contrast-enhanced computed tomography imaging from a separate cohort of patients with colorectal cancer metastatic to liver, and demonstrate accurate model predictions of individual patient responses (average relative error = 15%). Here, patient-specific data from either in vivo imaging or histopathology drives output of the model’s formulas. Values obtained from standard clinical diagnostic measurements for each individual are entered into the model, producing patient-specific predictions of tumor kill after chemotherapy. Clinical
Title: Agent based model reveals dichotomous regulation of immune cells by TGF-β1 and IL10 in a Tuberculosis Granuloma

Abstract:

Mycobacterium tuberculosis (Mtbd) is the pathogenic bacterium that causes tuberculosis (TB), one of the most lethal infectious diseases in the world. Developing new therapies requires a better understanding of the complex host immune response to infection, including dissecting the processes leading to formation of granulomas, the dense cellular lesions associated with TB. In this work we pair experimental and computational modeling studies to explore cytokine regulation in the context of TB. We use our next-generation hybrid multi-scale model of granuloma formation (GranSim) to capture molecular, cellular, and tissue scale dynamics of granuloma formation. We are able to perform immunological studies using GranSim which would be extremely challenging or impossible in vivo. From these studies, we identify a dichotomous regulation of cytotoxic T cells and macrophages by TGF-β1 and IL-10, respectively. This dichotomous regulation has been indicated for myeloid and lymphoid cell lineages in studies outside of TB. Our findings suggest that increasing cytotoxic T cell effector functions may increase bacterial clearance in granulomas, and highlight new potential therapeutic targets for treating TB. We identify TGF-β1 as a major inhibitor of cytotoxic T cell effector function in granulomas and show that deletion of TGF-β1 from the system results in improved bacterial clearance and lesion sterilization.

Hayley Warsinske, PhD
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SMB Abstract

A Multiscale Agent-Based Model of Triple-Negative Breast Cancer Stromal Heterogeneity: Contributions of Tumor Associated Macrophages and Cancer Associated Fibroblasts

Kerri-Ann Norton1*, Kideok Jin1, Aleksander S. Popel1,2

1Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, Maryland; 2Department of Oncology and Sidney Kimmel Comprehensive Cancer Center

Triple-negative breast cancer (TNBC) lacks the common receptors for estrogen, progesterone, and HER2 and is thus difficult to treat with targeted therapies. TNBC tumor development is influenced by the intrinsic properties of the tumor cells but also by its stromal microenvironment. Our laboratory studies breast cancer development focusing on heterogeneity of cancer cells and the tumor microenvironment. Breast cancer cells show heterogeneity in their intrinsic stem-like properties governing proliferation. The tumor stromal microenvironment is also heterogeneous, with differences in stromal infiltrates such as tumor associated macrophages (TAMs) and cancer associated fibroblasts (CAFs). Stromal infiltrates have been associated both with having pro- and anti-tumor effects. Thus, the interplay between breast cancer cells and their microenvironment is very complex needs to be better understood. Multiscale computational modeling is a powerful approach to unraveling this complexity.

Our laboratory has found experimentally that macrophages and fibroblasts secrete chemokines, such as interleukin 8 (IL8), upon treatment with MDA-MB-231 (MB231) tumor conditioned media (TCM). Using in vitro cell migration and proliferation assays, we found that MB231 cells co-cultured with macrophages and fibroblasts increased MB231 tumor cell migration and proliferation. We then validated the cancer cell-stromal cell crosstalk interactions in animal experiments in TNBC xenograft models, and explored therapeutic interventions. Based on these experimental data, we developed an agent-based model of triple negative breast cancer including the stem and progenitor cells, macrophages, and fibroblasts. TNBC cells are represented as objects that make decisions based on their intrinsic properties, such as their stem state, receptor levels, and their stromal microenvironment, such as proximity to macrophages and fibroblasts. A cell’s stem state governs its proliferation rate and the number of times it can replicate before becoming senescent. A cell’s receptor level governs its migration speed. The proximity to macrophages or fibroblasts influences a cell’s migration and proliferation rates.

Using agent-based modeling we examine not only the individual effects of stem cells, macrophages and fibroblasts on tumor development but also how they interact to promote tumorigenicity. We find that greater numbers of stem cells increase tumor growth and contributes to its invasive morphology. We also find that the large numbers of macrophages or fibroblasts increases the growth of the tumor. From these results, we make predictions as to which therapeutic targets have the most influence on tumor growth. Supported by NIH grant R01 CA138264 (ASP) and an American Cancer Society postdoctoral fellowship PF-13-174-01-CSM (KAN)

Email: knorton4@jhmi.edu
MS28: Modeling Heterogeneity in the Transmission of Pathogens among Hosts

SMB 2017 Mini-symposium Proposal

Organizer: Zhilan Feng, Department of Mathematics, Purdue University, zfeng@math.purdue.edu

Co-organizer: John Glasser, Centers for Disease Control and Prevention, jglasser@cdc.gov

Title: Modeling Heterogeneity in the Transmission of Pathogens among Hosts

Summary:
To reliably assess the potential impact of public health interventions, models must be capable of reproducing observed disease dynamics. Hosts differ in susceptibility to infection and infectiousness once infected. And their contacts vary with age, gender or location. To reproduce observed dynamics, models must capture this heterogeneity. Multiple approaches are employed, with however little apparent regard for their respective strengths and weaknesses. In any given situation, one must be best for determining the most effective or cost-effective means of mitigating transmission of pathogens among hosts. But which approach is best may depend on context. How finely heterogeneity must be modeled to reproduce disease dynamics determines whether analysis is possible or simulation is necessary. But how finely must heterogeneity be modeled?

Intended Audience:
Population biologists, epidemiologists, and mathematicians who support sound public health policy-making.

Speakers and affiliations:
Julien Arino, University of Manitoba

Sara Del Valle, Los Alamos National Laboratory

Fred Brauer, University of British Columbia

Vittoria Colizza, French National Institute of Health and Medical Research

Andrew Hill, Centers for Disease Control and Prevention
Schedule:

- **Effect of connections between households on the spread of an infectious pathogen**
  Julien Arino*, Ryan Sherbo
  3:30 - 4:00

- **An epidemic model with superspreaders**
  Fred Brauer
  4:00 - 4:30

- **Impact of heterogeneous changes in contacts and travels on seasonal influenza spread**
  Giancarlo De Luca, Kim Van Kerckhove, Pietro Coletti, Chiara Poletto, Nathalie Bossuyt, Niel Hens, Vittoria Colizza*
  4:30 - 5:00

- **Modeling Zika epidemics in South and Central America**
  Deborah Shutt, Carrie Manore, Stephen Pankavich, Aaron Porter, Sara Del Valle*
  5:00 - 5:30

- **Implications for infectious disease models of heterogeneous mixing on control thresholds**
  Zhilan Feng, Andrew N. Hill*, John W. Glasser
  5:30 - 6:00
Effect of connections between households on the spread of an infectious pathogen

Julien Arino\textsuperscript{1*} and Ryan Sherbo\textsuperscript{1}

\textsuperscript{1}Department of Mathematics, University of Manitoba, Winnipeg, Manitoba R3T 2N2, Canada. Julien.Arino@umanitoba.ca (JA) and sherbo.ryan@gmail.com (RS)

\* Presenter

Small isolated communities such as the ones found in the north of Canada seem to be more at risk of invasion by infectious diseases than larger communities. When a disease is established in this type of communities, it tends to persist longer. Taking the example of tuberculosis as a motivation, we investigate a model for the spread of an infectious disease in a community of households. We focus in particular on the role of the structure of connections between households and consider questions related to the heterogeneity of the interaction graph versus its size.
An epidemic model with superspreaders

Fred Brauer, University of British Columbia. brauer@math.ubc.ca

It appears that superspreading may be common in epidemics. We analyze a simple compartmental model for superspreading, and there are indications that such a model produces fewer disease cases than a simple homogeneous mixing model with the same reproduction number.
Impact of heterogeneous changes in contacts and travels on seasonal influenza spread

Giancarlo De Luca\textsuperscript{1}, Kim Van Kerckhove\textsuperscript{2}, Pietro Coletti\textsuperscript{2}, Chiara Poletto\textsuperscript{1}, Nathalie Bossuyt\textsuperscript{3}, Niel Hens\textsuperscript{2,4}, Vittoria Colizza\textsuperscript{1,5,*}

\textsuperscript{1}Sorbonne Universites, UPMC Univ. Paris 06, INSERM, Institut Pierre Louis d’Epidemiologie et de Sante Publique (IPLESP UMR S 1136), F-75012, Paris, France.
\textsuperscript{2}Interuniversity Institute for Biostatistics and statistical Bioinformatics, Hasselt University, Agoralaan Gebouw D, B-3590, Diepenbeek, Belgium.
\textsuperscript{3}Scientific Institute of Public Health (WIV-ISP), Public health and surveillance Directorate, Epidemiology of infectious diseases Service, Rue Juliette/Wytsmanstraat 14, B-1050, Brussels, Belgium.
\textsuperscript{4}Centre for Health Economics Research and Modelling Infectious Diseases, Vaccine and Infectious Disease Institute, University of Antwerp, Universiteitsplein 1, B-2610, Wilrijk, Belgium.
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*Presenter

The spread of seasonal influenza is thought to depend on biological, environmental and behavioral aspects. The rhythm imposed by the school calendar with breaks throughout the winter period is known to alter mixing patterns and travel behaviors of individuals. Here we aim to assess how these age-specific changes affect influenza spatial spread and its impact on the population. We built a spatially structured metapopulation model applied to Belgium, accounting for age-specific social mixing and travel behavior, as well as associated changes over time. Four types of calendar days are considered – regular week, regular weekend, holiday week, holiday weekend (with ‘regular’ referring to non-holiday periods). The model is parameterized with demographic, contact and travel data for Belgium and calibrated to the 2008/2009 influenza season. Holidays considerably delay the peak of the season and mitigate its impact. Changes in mixing patterns are responsible for the observed effects, whereas changes in travel behavior do not alter the epidemic. Weekends are important too in slowing down the season by periodically dampening transmission. Our findings highlight the need to quantify changes in the way individuals establish contacts over time in different demographic and epidemic contexts to accurately reproduce influenza dynamics. They also suggest strategic policies in the distribution of holiday periods to minimize the epidemic impact.
Modeling Zika epidemics in South and Central America

Deborah Shutt¹, Carrie Manore², Stephen Pankavich³, Aaron Porter⁴, Sara Del Valle⁵

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* Presenter

Abstract: As South and Central American countries prepare for increased birth defects from Zika virus outbreaks and plan for mitigation strategies to minimize ongoing and future outbreaks, understanding important characteristics of Zika outbreaks and how they vary across regions is a challenging and important problem. We developed a mathematical model for the 2015 Zika virus outbreak dynamics in Colombia, El Salvador, and Suriname. An important model input is the at-risk susceptible population, which can vary with a number of factors including climate, elevation, population density, and socio-economic status. We informed this initial condition using the highest historically reported dengue incidence modified by the probable dengue reporting rates in the chosen countries. The model indicated that a country-level analysis was not appropriate for Colombia. Our results show that the reproductive number for Zika ranges between 4 and 6 for El Salvador and Suriname with a median of 4.3 and 5.3, respectively. We estimated the reporting rate to be around 16% in El Salvador and 18% in Suriname with estimated total outbreak sizes of about 73,400 and 21,650 people, respectively. Our model highlights the importance of regional level data to capture the true dynamics of disease outbreaks as well as the need for better data collection approaches to increase reporting rates.
Implications for infectious disease models of heterogeneous mixing on control thresholds

Zhilan Feng\textsuperscript{1}, Andrew N. Hill\textsuperscript{2}, John W. Glasser\textsuperscript{3}

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\textsuperscript{2}Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA. \texttt{fyu7@cdc.gov}
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*Presenter

Mixing among sub-populations, as well as heterogeneity in characteristics affecting their reproduction numbers, must be considered when evaluating public health interventions to prevent or control infectious disease outbreaks. In this talk, we model preferential within- \textsuperscript{and} proportional among-group contacts in compartmental models of disease transmission and derive results for the overall effective reproduction number ($R_v$) assuming different levels of vaccination in the sub-populations. Specifically, we unpack the dependency of $R_v$ on the fractions of contacts reserved for individuals within one’s own subgroup and show that $R_v$ increases as this fraction increases in a given sub-population. These considerations lead to our proposing the gradient of $R_v$ with respect to subgroup vaccination fractions as a measure by which to evaluate interventions. This work is based on and extends Feng \textit{et al.}, J. Theor. Biol. 386 (2015) 177–187.
Title: Modeling Cancer Immunotherapies

Organizers:

- Lisette de Pillis, Mathematics Department, Harvey Mudd College. depillis@g.hmc.edu.
- Ami Radunskaya, Mathematics Department, Pomona College. aer04747@pomona.edu.

Description: Cancer Immunotherapy was heralded as the “Breakthrough of the Year” in 2013 by Science Magazine. Despite some promising outcomes, overall results from clinical trials have been disappointing; the reasons for these mixed results are myriad. Mathematical models that describe tumor growth in tissue, the immune response, and the administration of combination therapies can suggest treatment strategies that optimize treatment efficacy and minimize negative side-effects. In particular, stimulating an inflammatory response can result in an immuno-suppressive environment, where the tumor cells are able to block the immune cells’ anti-tumor activity. New treatments have now been developed to block the immune blockers. How should the immune-stimulation and these blockers be administered? The big questions are, as they always have been, How much? How often? In which order? In this session, speakers will present several approaches to answering these challenging questions.
Schedule:

- **Mathematical Modeling of Combination Therapy with Cancer Vaccine and anti-PD-1**
  Avner Friedman
  3:30 - 3:55

- **Mathematical model for checkpoint blockade therapy in cancer treatments**
  Collin Zheng*, Peter Lee, Peter Kim
  3:55 - 4:20

- **Analyzing cancer therapeutic robustness. oncolytic viruses with immunotherapy**
  Jana Gevertz
  4:20 - 4:45

- **How does pressure within a tumour affect the outcome of cancer treatment?**
  Adrianne Jenner*, Peter Kim
  4:45 - 5:10

- **The mathematical implications of a continuum of differentiation states in hematopoiesis**
  Russel Rockne
  5:10 - 5:35
Author:
Avner Friedman
Department of Mathematics, The Ohio State University, USA
afriedman@math.osu.edu

Title:
Mathematical Modeling of Combination Therapy with Cancer Vaccine and anti-PD-1

Abstract:
Effective T cells kill cancer cells, but they are inhibited by checkpoints, such as PD-1. When its ligand PD-L1 combines with membrane protein PD-1 on the T cell, the T cell activity is blocked. Recently several anti-PD-1 drugs have been approved by FDA, and they offer exciting opportunities in cancer therapy. In this talk we consider a combination therapy of cancer, with one drug, a vaccine, which activates dendritic cells, so that they induce more T cells to infiltrate the tumor, and another drug, a checkpoint inhibitor anti-PD-1, which enables the T cells to remain active against the cancer cells. To address the question of synergy between the two drugs, we develop a mathematical model, by a system of partial differential equations, which includes dendritic and cancer cells, CD4+ and CD8+ T cells, IL-12 and IL-2, CM-CSF produced by the vaccine, and a T cell checkpoint inhibitor associated with PD-1. We use the model to explore the efficacy of the two drugs, separately and in combination, and compare the simulations with data from mouse experiments. We next introduce the concept of synergy between the drugs and develop a synergy map which suggests in what proportion to administer the drugs in order to achieve the maximum efficacy.

This is joint work with MBI postdoctoral fellow Xinlan Lai.
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Peter Kim
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Title:
Mathematical model for checkpoint blockade therapy in cancer treatments

Abstract:
The human immune system has checkpoint proteins, such as CTLA4 and PD1, that keep it from attacking healthy cells. Unfortunately, cancer cells have the ability to take advantage of these checkpoints to avoid being attacked by the immune system, thereby evading some of the most potent antitumor weapons in the immune arsenal, such as the cytotoxic T-lymphocyte (CTL) or killer T cell. As a result, the development of antibody drugs suppressing these checkpoints is becoming an important part of the fight against cancer in immunotherapy. Despite promising clinical results, an unexplained phenomenon has been the mysterious delay of several months prior to the drugs taking on a tangible therapeutic effect. Such a delay may very well reflect the notion that the suppression of checkpoints plays only a partial role in unleashing a T-cell response. Two other factors which play an integral role in unleashing a T-cell response is tumour antigen simulation, along with a co-stimulatory signal provided by an antigen presenting cell (APC) typically a dendritic cell (DC). We present an ordinary differential equation model that incorporates both these positive and inhibitory factors together to shed insight onto the mechanisms of these novel checkpoint blockade drugs. Such biological insights may offer potential strategies on how to increase the efficacy of checkpoint blockade therapies in the future, as both a lone treatment and in combination with other anticancer treatments.
Author:
Jana Gevertz
Department of Mathematics and Statistics, College of New Jersey, USA
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Title:
Analyzing cancer therapeutic robustness: oncolytic viruses with immunotherapy

Abstract:
Oncolytic viruses (OVs) are an emerging class of therapeutic agents that can directly trigger tumor cell lysis while also acting as vectors for delivering beneficial genes, such as cytokines, to the tumor site. Such immuno-enhancing OVs have been shown to result in significant tumor de-bulking in a mice model of melanoma, and these effects were enhanced when dendritic cells (DCs) are added to the treatment protocol. This experimental system led to questions about the optimal dosing order for these two drugs, and whether we could expect a robust tumor-killing response across the population under study. With these questions in mind, this talk will introduce a platform that integrates experimental data, mathematical modeling and statistical analyses for identifying robust optimal treatment protocols. The methodology begins with the time-course experimental data from a sample population, and a mathematical model that gets fit to aggregate data from that sample population. Using nonparametric statistics, the sample population is amplified and utilized to create a large number of virtual populations. Robustness is then assessed by identifying and analyzing the optimal therapy (perhaps restricted to a set of clinically-realizable protocols) across each virtual population. Application of this methodology to experimental data on treating melanoma-bearing mice with oncolytic viruses and dendritic cell vaccines (a) showed that every scheduling variant of the experimentally-utilized treatment protocol is fragile (non-robust), and (b) discovered an alternative region of dosing space (lower oncolytic virus dose, higher dendritic cell dose) for which a robust optimal protocol exists.
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Peter Kim
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Title:
How does pressure within a tumour affect the outcome of cancer treatment?

Abstract:
Interstitial pressure or elevated pressure within tumour’s has been identified as one of the major culprits impeding effective cancer treatments such as immunotherapy. Tumour pressure is known to cause heterogeneous intratumoural distribution of cancer treatments and increase the metastatic potential of tumours. Reducing tumour pressure has been shown experimentally to enhance the uptake of therapies as well their homogeneous distribution. So how instrumental is tumour pressure in reducing treatment efficacy? In this work we model the spatial distribution of treatment and the effect of pressure on treatment diffusibility. We use a connected network of compartments with each compartment described by a system of ODEs. Investigations are undertaken into the optimisation potential of pressure reducing treatments combined with alternate treatment application profiles to discern how to enhance homogeneous treatment diffusion without allowing the formation of metastasis. This work addresses an area possibly lacking in investigation and through deriving an appropriate mathematical model we show the impact of tumour pressure on immunotherapy and cancer treatments a like.
Author:
Russel Rockne
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Title:
The mathematical implications of a continuum of differentiation states in hematopoiesis

Abstract:
Mathematical descriptions of cell differentiation from a stem to a differentiated state typically describe distinct populations of cells, whether in discrete or continuous time, as deterministic or stochastic systems. Current technology used to analyze biological systems, however, shows that the biological categories that are used to identify cells in states of differentiation are not mutually exclusive, nor are they unique. Because of this, there is a methodological and mathematical gap in how we describe the evolution of a continuum of cell differentiation states. As increasing amounts of biological data become available, the current discrete-states model structures will not be sufficient to capture and reflect new biological knowledge as it emerges. Here we present hematopoietic cell differentiation in a continuous phenotype space defining trajectories of differentiation though nonlinear dimension reduction and discuss the mathematical implications of the observed continuum of differentiation states.
MS30: Disease and Control, Part I

SMB 2017 Mini-symposium Submission

Organizer: Seema Nanda, seema.nanda@dartmouth.edu

Co-organizer: Adnan Khan, adnan.khan@lums.edu.pk

Title: Disease and Control, Part 1

Compartment models have found wide applications in in-vivo and in-vitro modeling of dynamics of diseases and their transmission. Therefore modeling of disease control is typically based on these compartmental models using ordinary and partial differential equations and some Markov process models. Control of disease includes transmission control and therapeutic control in non-infectious and infectious diseases, in addition to other formulations of disease control. In this symposium we will bring together mathematicians, statisticians and biologists studying the control of disease. A significant gap is the application of results from theoretical control problems to biological experiments. We aim to enhance interdisciplinary understanding and establish collaborations across these fields to address both the above gaps. Further, we bring together people working in this area from a variety of geographical regions who bring modeling experience to solve local problems.
Schedule:

- **A model describing the Transmission Dynamics of Zika Fever**
  Mudassar Imran*, M Usman, M Ahmad, A Khan
  10:30 - 11:00

- **A model to assess the effect of vaccine compliance on Human Papillomavirus infection and cervical cancer**
  Tufail Malik*, Oluwaseun Sharomi
  11:00 - 11:30

- **An alternative to cART therapy for HIV**
  S. Nanda*, V Ratti, D Wallace
  11:30 - 12:00

- **Free-virus and cell-to-cell transmission in models of equine infectious anemia virus infection**
  Elissa J. Schwartz*, Linda J. S. Allen
  12:00 - 12:30
Title: A model describing the Transmission Dynamics of Zika Fever:

Author: Mudassar Imran* (Imran.M@gust.edu.kw), M Usman, M Ahmad, A Khan

Affiliation: Gulf University of Science and Technology, Kuwait,
e-mail: Imran.M@gust.edu.kw

In this paper, a deterministic model is proposed to perform a thorough investigation of the transmission dynamics of Zika fever. Our model, in particular, takes into account the effects of horizontal as well as vertical disease transmission of both humans and vectors. The expression for basic reproductive number $R_0$ is determined in terms of horizontal as well as vertical disease transmission rates. An in-depth stability analysis of the model is performed, and it is consequently shown, that model is locally asymptotically stable when the basic reproduction number $R_0 < 1$. In this case, there is a possibility of backward bifurcation in the model. With the assumption that total population is constant, we prove that the disease-free state is globally asymptotically stable when $R_0 < 1$. It is also, shown that disease strongly uniformly persists when $R_0 > 1$ and in this case there exists an endemic equilibrium which is unique if the total population is constant. The endemic state is locally asymptotically stable when $R_0 > 1$. 
Title: A model to assess the effect of vaccine compliance on Human Papillomavirus infection and cervical cancer.

Author: Tufail Malik* (tufail.malik@kustar.ac.ae) and Oluwaseun Sharomi

Affiliation: Khalifa University, Abu Dhabi

Abstract: Three doses of a Human Papillomavirus (HPV) vaccine are recommended for both males and females, and compliance is a major challenge. A two-sex deterministic model is presented where the female population is further stratified into two age groups: the first group at a higher risk for new HPV infection, not likely to develop cervical cancer, and subject to three doses of an HPV vaccine, and the second age group with reduced chances of acquiring new infections but at a higher risk for developing cervical cancer. The model exhibits a backward bifurcation which is caused due to the imperfect HPV vaccine. For the case of a perfect vaccine, the disease-free equilibrium is proved to be globally asymptotically-stable when the effective reproduction number $R_0$ is less than unity. Multiple endemic equilibria may exist when $R_0 > 1$. It is shown through numerical simulations that vaccine compliance is necessary for the reduction of HPV infections and cervical cancer.
Title: An alternative to cART therapy for HIV

Author: S. Nanda* (Seema.Nanda@dartmouth.edu), V Ratti and D Wallace

Affiliation: Dartmouth College, Hanover, NH

Abstract:

We present a mathematical model that takes into account treatment for HIV using a proposed new CRISPR/CAS gene therapy approach. This approach could eliminate the need for the current combined anti-retroviral therapy (cART). Our dynamical systems model takes into account the hard to eliminate latent reservoir of infected HIV cells, which are a barrier to elimination of the disease with current treatments. We show the possibility of replacing cART therapy with gene edited cells which could eventually replace the infected CD4 cells.
Equine infectious anemia virus (EIAV) is a lentivirus in the retrovirus family that infects horses and ponies. Two strains, referred to as the sensitive strain and the resistant strain, have been isolated from an experimentally-infected pony. The sensitive strain is vulnerable to neutralization by antibodies whereas the resistant strain is neutralization-insensitive. The sensitive strain mutates to the resistant strain. EIAV may infect healthy target cells via free virus or alternatively, directly from an infected target cell through cell-to-cell transfer. The proportion of transmission from free-virus or from cell-to-cell transmission is unknown. A system of ordinary differential equations (ODEs) is formulated for the virus-cell dynamics of EIAV. In addition, a Markov chain model and a branching process approximation near the infection-free equilibrium (IFE) are formulated. The basic reproduction number $R_0$ is defined as the maximum of two reproduction numbers, $R_{0s}$ and $R_{0r}$, one for the sensitive strain and one for the resistant strain. The IFE is shown to be globally asymptotically stable for the ODE model in a special case when the basic reproduction number is less than one. In addition, two endemic equilibria exist, a coexistence equilibrium and a resistant strain equilibrium. It is shown that if $R_0 > 1$, the infection persists with at least one of the two strains. However, for small infectious doses, the sensitive strain and the resistant strain may not persist in the Markov chain model. Parameter values applicable to EIAV are used to illustrate the dynamics of the ODE and the Markov chain models. The examples highlight the importance of the proportion of cell-to-cell versus free-virus transmission that either leads to infection clearance or to infection persistence with either coexistence of both strains or to dominance by the resistant strain.
MS31: Quantitative approaches to developmental biology

Society for Mathematical Biology Annual Meeting 2017 – Developmental Biology Minisymposium

Organizer
Ruth Baker – Mathematical Institute, University of Oxford (baker@maths.ox.ac.uk)

Title
Quantitative approaches to developmental biology

Summary
The dramatic advances made in molecular biology and imaging techniques in recent years have led to an unparalleled flood of experimental data on increasingly fine spatial and temporal scales. We can visualize and quantify signalling molecules and force generating structures at the single-cell level, and below, yet these data alone do not explain how an organism is built. Developing embryos are transformed from a ball of cells with no inherent structure into the range of exotic organisms that make up the living world by a stitching together of the myriad effects of cell signalling with complex cell and tissue biomechanics. However, the complex nature of morphogenetic processes, with driving mechanisms taking place across molecular, cellular and tissue level scales, makes them the focus of studies from a range of different cell-biological perspectives, leading to a comprehension that is, at best, fragmented. It is clear that to make best use of the insights gained from these multi-modal, quantitative experimental studies we must fully embed theoretical methodologies into the toolkit we have to explore developmental biology processes.

The challenge for the modelling community is now to develop and simulate biologically accurate models, extract quantitative data from experiments, and test and validate models using these quantitative data, as part of the predict-test-refine-predict cycle essential in biology. However, there are many challenges remaining in each of these areas. The aim of this first activity of the Developmental Biology SMB subgroup is to bring together high-profile researchers in the field who will showcase exemplar interdisciplinary, quantitative studies in developmental biology. This will raise the profile of quantitative approaches to development within the SMB, encourage new members to join the subgroup and work in the area, and, together with the lunchtime mixer event, provide a platform for new interactions between SMB members working in the area.

Schedule (including order of speakers, tentative title and talk duration)
- Qixuan Wang (30 minutes)
- Roeland (30 minutes).
- Philip Murray (30 minutes).
- David Umulis. (30 minutes).
Schedule:

- *Noise regulates tissue and embryo development in response to spatial information*
  Qixuan Wang*, Qing Nie
  10:30 - 11:00

- *Multiscale, computational modeling of angiogenesis: tip-cell overtaking and cell-ECM interactions*
  Roeland Merks
  11:00 - 11:30

- *Data-driven modelling of the somitogenesis clock*
  Philip Murray*, Lucas Morales, Kim Dale
  11:30 - 12:00

- *Mathematical modeling and multi-objective optimization of BMP-mediated patterning in developing systems*
  David Umulis*
  12:00 - 12:30
Title: Noise regulates tissue and embryo development in response to spatial information

Authors: Qixuan Wang* (qixuanw@uci.edu), Qing Nie (qnie@math.uci.edu)

Institution: Department of Mathematics, University of California Irvine

Abstract:

In tissue growth and morphogenesis, cells make fate decisions in response to chemical gradients, many of which incorporate spatial information that instruct the future development of tissues and structures. However, these gradients are noisy at any level, raising the question of how cells read and respond faithfully to these spatial-information-incorporated chemical stimuli. Recently, new experimental data on early embryo development indicates that noise may play an important role in the regulation of cell fate decisions. We have developed hybrid spatial models to study how noise helps cells make fate decisions that, in return, maintain further system development. In particular, two systems are studied: zebrafish hindbrain rhombomere formation; and early mammalian embryo development. Our approaches allow us to recognize and validate mechanisms and principles underlining spatial cell fate decision dynamics during development and growth.
Title: Multiscale, computational modeling of angiogenesis: tip-cell overtaking and cell-ECM interactions

Authors: Roeland Merks* (roeland.merks@cwi.nl)

Institution: Life Sciences group, Centrum Wiskunde & Informatica, Amsterdam, and Mathematical Institute, Leiden University

Abstract:

Angiogenesis, the growth of new blood vessels from existing ones through sprouting or splitting, is crucial for a range of physiological or pathological phenomena, ranging from wound healing to tumor development. In order to achieve fine-level control of angiogenesis in these mechanisms, we are developing multiscale, computational models of collective endothelial cell behavior during angiogenesis based on the cellular Potts model. In the first part of the talk, we will discuss cell behavior at the front of advancing angiogenic sprouts. The traditional view is that a specialized endothelial cell, the tip cell, leads the sprout. It is followed by a second type of endothelial cell, called the stalk cell. However, two experimental groups have shown independently that tip and stalk cell fates are reversible, and that cells compete for the tip cell position, a phenomenon coined ‘tip cell overtaking’. The groups could not agree on whether tip cell overtaking is actively regulated genetically, through the Notch1-Dll4 pathway, or whether it is due to non-functional ‘cell mixing’. In support of the ‘cell mixing’ idea, tip cell overtaking emerges naturally in our models of angiogenesis. After introducing a dynamic Notch1-Dll4 model into each cell, we found that our ‘cell mixing’ model of tip cell overtaking can reproduce the evidence in favor of the ‘genetic control’ model. The two initial cell-based models of angiogenesis that we have used in these studies of tip-cell overtaking did not include the extracellular matrix (ECM), the jelly materials (e.g., fibrin or collagen) that the endothelial cells live in. In vitro studies have shown that the chemical composition and the mechanical properties of the ECM are key to the ability of endothelial cells to form blood vessel-like structures. The second part of the talk will, therefore, discuss our attempts to model the mechanical and chemical cell-ECM interactions, and explain how the extracellular matrix could control and coordinate endothelial cell behavior during angiogenesis.
Title: Data-driven modelling of the somitogenesis clock

Authors: Philip Murray* (pmurray@dundee.ac.uk), Lucas Morales (l.j.moralesmoya@dundee.ac.uk), Kim Dale (K.Dale@dundee.ac.uk)

Institution: University of Dundee

Abstract:

During somitogenesis the vertebrate embryo segments at regular time intervals. Underlying this periodicity is a molecular oscillator known as the somitogenesis clock. Using real-time reporters for clock gene expression, the dynamics of the clock can be experimentally interrogated, thus imposing constraints on theoretical models. In this talk I will present results from a collaborative project in which the effect of different drug treatments on the somitogenesis clock are recorded using a real-time reporter. I will then describe how mathematical models are used help to interpret the experimental data and explore underlying mechanisms.
Title: Mathematical modeling and multi-objective optimization of BMP-mediated patterning in developing systems.

Authors: David Umulis* (dumulis@purdue.edu)

Institution: Agricultural and Biological Engineering, Purdue University

Abstract:

Bone Morphogenetic Proteins (BMPs) act in developmental pattern formation as a paradigm of extracellular information that is passed from an extracellular morphogen to cells that process the information and differentiate into distinct cell types based on the morphogen level. Numerous extracellular modulators and feedback regulators establish and control the BMP signaling distribution along the dorsal-ventral (DV) embryonic axis in both Drosophila and zebrafish to induce space and time-dependent patterns of gene expression. To identify how the BMP patterning mechanism evolved in Drosophila vs. zebrafish, we have developed a new multi-objective optimization strategy. Since patterning in both systems relies on a common set of inhibitors and regulators, we developed a core-model and identified whether there is a single set of biophysical parameters that, when fit to both Drosophila and zebrafish data, is able to explain both patterning mechanisms. Intriguingly, there is a significant trade-off between the model fitness and different parameters are required to be independently tuned for a single mechanism to fit both types of data. We extended the framework and identified the minimal set of parametric differences that must be present for one core model to fit both patterning contexts.
MS32: Stage-structured Population Models in Biology

Organizer: John Nardini

Stage-structured population models, in which one or more physiological traits are incorporated into a partial differential equation to distinguish individuals, are an active area of research in math biology. These models are particularly useful due to their ability to capture the heterogeneous nature of a biological population. Areas of application covered in this minisymposium include disease transmission, epidermal wound healing, and species invasion and evolution. The models considered in these studies have naturally lent themselves into mathematical investigations of wave propagation, semigroups, stability analysis, traveling-wave solutions, and delay differential equations that extend previous results from their corresponding models with homogeneous populations.

The aim of this minisymposium is to highlight recent advances in the study of stage-structured population models and their applications. This minisymposium will facilitate the extension of current studies of stage-structured models while also providing an introduction for researchers interested in pursuing their own stage-structured population studies.
Schedule:

- *Investigation of a Structured Fisher’s Equation with Applications in Biochemistry*
  John Nardini*, David M. Bortz
  10:30 - 11:00

- *Evolution of Dispersal and the Cane Toads equation*
  Emeric Bouin
  11:00 - 11:30

- *An Age-Structured Model for the Coupled Dynamics of HIV and HSV-2*
  Christina Alvey*, Georgi Kapitanov, Katia Vogt-Geisse, Zhilan Feng
  11:30 - 12:00
**Title:** Investigation of a Structured Fisher’s Equation with Applications in Biochemistry

**Authors and Affiliations:** John Nardini* – University of Colorado, Boulder – john.nardini@colorado.edu
David M. Bortz – University of Colorado, Boulder – dmbortz@colorado.edu

**Abstract:** Recent biological research has sought to understand how biochemical signaling pathways, such as the mitogen-activated protein kinase (MAPK) family, influence the migration of a population of cells during wound healing. Fisher’s Equation has been used extensively to model experimental wound healing assays due to its simple nature and known traveling wave solutions. This partial differential equation with independent variables of time and space cannot account for the effects of biochemical activity on wound healing, however. To this end, we derive a structured Fisher’s Equation with independent variables of time, space, and biochemical pathway activity level and prove the existence of a self-similar traveling wave solution to this equation. We also consider a more complicated model with different phenotypes based on MAPK activation and numerically investigate how various temporal patterns of biochemical activity can lead to increased and decreased rates of population migration.
**Title:** An Age-Structured Model for the Coupled Dynamics of HIV and HSV-2

**Authors and Affiliations:** Christina Alvey* - Mount Saint Mary College - christina.alvey@msmc.edu
Georgi Kapitanov - The University of Iowa - georgi-kapitanov@uiowa.edu
Katia Vogt-Geisse - Universidad Adolfo Ibáñez - katia.vogt@uai.cl
Zhilan Feng - Purdue University - fengz@purdue.edu

**Abstract:** Evidence suggests a strong correlation between the prevalence of HSV-2 and the perseverance of the HIV epidemic. HSV-2 is an incurable viral infection characterized by periodic reactivation. We model the co-infection of the two viruses by incorporating a time-since-infection variable to account for the alternating periods of infectiousness of HSV-2. We derive the basic reproduction numbers for each virus to determine whether they become endemic in the absence of the other disease. We also derive the invasion reproduction numbers that determine whether or not a virus can invade into a population in which the other disease is endemic. The calculations of the invasion reproduction numbers suggest a new aspect in their interpretation – the class from which the initial disease carrier arises is important for understanding the invasion dynamics and biological meanings of the expressions of the reproduction numbers. A sensitivity analysis is conducted to examine the role of model parameters in influencing the model outcomes.
MS33: Confronting Biological Models with Data: Dealing with Complexity and Sparsity I

Minisymposium Title: Confronting Biological Models with Data: Dealing with Complexity and Sparsity I
Organizer: Richard Schugart, richard.schugart@wku.edu
Co-Organizer: Noelle G. Beckman, nbeckman@sesync.org

Summary: Models range from strategic models that require large amounts of data to parameterize for prediction to tactical models that require less data but are poorer at extrapolating beyond the range of the data as they are conceptually simpler. With advances in environmental sensors, imaging, remote sensing, and coordinated efforts to curate data in publicly accessible repositories, the quantity of data is rapidly increasing in the environmental and health sciences. However, as data increases into the realm of big data, mathematical and statistical challenges arise to integrate these data with mathematical models for better understanding and prediction. Challenges in effectively synthesizing data with mathematical models include simplifying often complex data with minimal loss of information and handling sparsity in data as the size and complexity of data increases. As data from experimental and observational studies can inform the development of models, models can be used to inform data collection. In this first session, speakers will present a variety of mathematical and statistical advances in merging data with models for understanding and prediction in human health and ecology.
Schedule:

- *Modeling Across Scales: From Data Sparsity to Data Overload*
  Juan B. Gutierrez
  10:30 - 10:50

- *Combining tactical and strategic approaches to predict vector-borne disease*
  Leah R. Johnson
  10:50 - 11:10

- *Complexity reduction for stochastic network models in biology*
  Deena Schmidt*, Roberto Galan, Peter Thomas
  11:10 - 11:30

- *Modeling Differences Between Patients with Diabetic Foot Ulcers*
  Richard C. Schugart
  11:30 - 11:50

- *Optimal Experimental Design for Daphnia magna Age-Structured Models*
  Erica M. Rutter*, H.T. Banks, Gerald LeBlanc, Kevin B. Flores
  11:50 - 12:10
Authors:
Juan B. Gutierrez, University of Georgia, jgutierr@uga.edu

Title: Modeling Across Scales: From Data Sparsity to Data Overload

Abstract: The types of models commonly found in biomathematics are usually categorized in a few classes, and their implementation is normally constrained by data availability thus leaving some problems in the theoretical realm (i.e. “solve the problem right” instead of “solve the right problem”). In this talk we will explore canonical examples of how practical considerations about data availability shape the questions that could be answered mathematically. The context will be the infectious disease malaria, but the considerations about analysis, computability, and reproducibility emerging from looking at the multi-scale analysis of malaria are of ample applicability and go beyond the realm of infectious disease. At its most fundamental level, it is a question about the nature of mathematical biology and the definitions that emerge from the consensus of the community.
Authors:
Leah R. Johnson, Virginia Tech, lrjohn@vt.edu

Title: Combining tactical and strategic approaches to predict vector-borne disease

Abstract: There are a variety of approaches to modeling and making predictions about the dynamics of infectious disease. For instance, one can take a strategic/mechanistic approach that primarily concerns itself with determining what types of processes can cause certain patterns. Strategic models often require large amounts of data to parameterize them and make them useful for prediction. On the other extreme are tactical/phenomenological models, like regressions, that usually focus on fitting a pattern without elucidating why those patterns exist. Tactical models, while often conceptually simpler, can be poor for extrapolating beyond the range of the data. Thus each approach has its strengths and weaknesses in terms of data needed to parameterize and validate the model and the types of predictions that we can make using them. I talk about the open challenge of how to use data at different resolutions with models that incorporate both mechanistic and strategic elements to improve prediction. In particular I focus on building models to prediction the dynamics of vector-borne diseases at different spatial and temporal scales using Dengue in the Americas as a case study.
Authors:  
Deena Schmidt*, University of Nevada, Reno, drschmidt@unr.edu  
Roberto Galan, Case Western Reserve University, rfgalan@case.edu  
Peter Thomas, Case Western Reserve University, pjthomas@case.edu

Title: Complexity reduction for stochastic network models in biology

Abstract: Markov processes are widely used to model the dynamics of biological processes transitioning among multiple states. Complexity reduction aims to capture the essential dynamics of the process via a simpler representation, with minimal loss of accuracy. The stochastic shielding approximation is a novel dimension reduction method that has been used to simplify stochastic network models arising in neuroscience, such as randomly gated ion channel models. Here we explore the robustness of the stochastic shielding approximation under conditions of timescale separation, population sparsity, and “bursty” ion channel behavior. We also give examples of how this method can be applied to other physiological processes in biology.
Authors: Richard C. Schugart, Western Kentucky University, richard.schugart@wku.edu

Title: Modeling Differences Between Patients with Diabetic Foot Ulcers

Abstract: In this work, we quantify differences in healing responses between type-II diabetic patients with foot ulcers. This work builds off of our previous publication (Krishna et al., B Math Biol, 2015), where we formulate a mathematical model to describe healing responses using averaged time-course data from another study (Muller et al., Diabet Med, 2008). In Muller’s work, they collect data from 16 patients with type-II diabetes. In addition to recording wound areas, Muller also measures levels of matrix metalloproteinases and their inhibitors at Weeks 0, 1, 2, 4, 8, and 12, collected from wound fluid. The patients are divided into two groups categorized as “good healers” and “poor healers” dependent upon the healing response at the four-week point. In our previous work, we use the average data to calibrate our mathematical model and quantify differences between the two groups. In our current work, we have calibrated our mathematical model for each individual patient and have quantified differences between these patients. In this presentation, we will discuss how our model has identified differences across patients using a variety of techniques.
Authors: Erica M. Rutter*, North Carolina State University, erutter@ncsu.edu  
H.T. Banks, North Carolina State University, htbanks@ncsu.edu  
Gerald LeBlanc, North Carolina State University, gal@ncsu.edu  
Kevin B. Flores, North Carolina State University, kbflores@ncsu.edu

Title: Optimal Experimental Design for Daphnia magna Age-Structured Models

Abstract: Daphnia magna is a species of water flea that has been studied extensively in ecotoxicology, aquatic ecology, and population modeling. Daphnids have been used as a biomonitor to assess potential adverse effects of pesticides and other chemicals on aquatic ecosystems. Currently, many experiments are performed at the level of individual daphnids, but more population studies are needed to investigate the relationship between individual level toxicity and ecosystem adversity. We performed longitudinal population experiments using Daphnia magna and used data to propose a continuously-structured population model that incorporates both density-dependent and density-independent fecundity and mortality rates. We fit our model using a generalized least-squares framework and estimate parameters and their confidence intervals.

Due to the extensive man-hours required to obtain population level data, we explore various methods of obtaining similarly informative data with less labor. First, we consider optimally designing our experiments in order to minimize the amount of data collected while ensuring that parameters may still be estimated with low uncertainty. Next, we describe methodology for more efficient data acquisition using digital imaging and neural networks.
MS34: Metastasis: Mathematical Modeling and Clinical Applications

Mini-symposium

Metastasis: Mathematical Modeling and Clinical Applications

Organizer: Dr. Leonid Hanin, Department of Mathematics and Statistics, Idaho State University, Pocatello, ID 83209-8085, USA; E-mail: hanin@isu.edu

Co-organizer: Dr. Thomas Hillen, Department of Mathematical and Statistical Sciences, University of Alberta, Edmonton, AB, T6G 2G1, Canada; E-mail: thillen@ualberta.ca

Summary: Metastasis is a systemic dissemination of solid cancer. It accounts for about 90% of all cancer-related deaths, with no definitive cure available. Thus, studying metastasis and designing effective therapeutic interventions is one of the most pressing scientific and health care problems. Metastasis is a complex multi-stage process that involves shedding of metastases by the primary tumor, their free circulation, dormancy of solitary cancer cells or micro-metastases in various secondary sites, escape from dormancy, angiogenesis induction, and active proliferation. These processes are largely unobservable, which makes mathematical modeling an indispensable tool for understanding the origins and natural history of metastatic cancer. The mini-symposium will focus on new mathematical models of metastasis, cancer cell proliferation and migration, systemic aspects of the interaction of metastases with the immune system, metastatic niches and cancer stem cells. The mini-symposium will also address clinical applications of these theoretical developments. In particular, effects of surgical removal of the primary breast tumor on metastatic progression, prognostic biomarkers of pancreatic cancer and immunity-modulating effects of resection and radiotherapy of primary and secondary tumors will be discussed.
Schedule:

- **A quantitative insight into metastatic relapse of breast cancer**
  Leonid Hanin*, Lyudmila Pavlova
  10:30 - 10:50

- **Mathematical modeling predicts PDAC morphology could be a biomarker for aggressive disease**
  John Lowengrub*, Eugene Koay, Vittorio Cristini, Huaming Yan
  10:50 - 11:10

- **Metastases might be the result of inflammatory processes by adapted immune cells**
  Leili Shahriyari*
  11:10 - 11:30

- **Perturbation of systemic tumor-immune dynamics in metastatic cancer**
  Rachel Walker*, Jan Poleszczuk, Heiko Enderling
  11:30 - 11:50

- **Modelling cancer spread with non-local birth-jump processes**
  Thomas Hillen
  11:50 - 12:10
A QUANTITATIVE INSIGHT INTO METASTATIC RELAPSE OF BREAST CANCER

Leonid Hanin*, Department of Mathematics and Statistics, Idaho State University, Pocatello, ID 83209-8085, USA; E-mail: hanin@isu.edu

Lyudmila Pavlova, Department of Applied Mathematics, St. Petersburg Polytechnic University, 195251 St. Petersburg, Russia; E-mail: lyu0510@gmail.com

ABSTRACT

Background. Metastatic relapse is the principal source of breast cancer mortality. The goal of the work is to uncover unobservable, yet clinically important, aspects of post-surgery metastatic relapse of breast cancer and to quantify effects of surgery on metastatic progression.

Methods. We classified metastases into three categories: (1) solitary cancer cells that were formed before or during surgery and either circulate in blood or are lodged at various secondary sites; (2) dormant or slowly growing avascular metastases; and (3) vascular secondary tumors. We developed a general mathematical model aimed at describing post-surgery dynamics of these three metastatic states. One parametric version of the model assumed that sojourn times of metastases in the three states are exponentially distributed while another was based on Erlang distribution. Model parameters were estimated from a sample of metastatic relapse or censoring times for 673 breast cancer patients treated with surgery.

Results. We estimated the expected number of metastases and mean sojourn times for the three states and found that both are decreasing with state number. We also computed the probability that metastatic relapse resulted from a metastasis in a given state at surgery. The values of these attribution probabilities suggest that under the Erlang model all three states have a considerable effect on metastatic relapse while in the case of exponential model this is true for states 1 and 2 only.

Conclusions. (1) In some patients metastasis occurred before surgery; (2) Our results confirm significance of metastatic dormancy; (3) According to the model, surgery stimulates escape from dormancy, promotes angiogenesis and accelerates metastatic growth in a fraction of breast cancer patients. Taken summarily, these findings call into question the benefits of primary tumor resection for certain categories of breast cancer patients.
MATHEMATICAL MODELING PREDICTS PDAC MORPHOLOGY COULD BE A BIOMARKER FOR AGGRESSIVE DISEASE

John Lowengrub* and Huaming Yan, University of California, Irvine, CA, USA; E-mails: lowengrb@math.uci.edu, huamingy@math.uci.edu

Eugene Koay, University of Texas MD Anderson Cancer Center, Houston, TX, USA; E-mail: EKoay@mdanderson.org

Vittorio Cristini, University of Texas Health Science Center, Houston, TX, USA; E-mail: Vittorio.Cristini@uth.tmc.edu

ABSTRACT

In this talk, we develop a tissue-level mathematical and computational model of pancreatic ductal adenocarcinoma (PDAC). PDAC is a heterogeneous disease that is generally associated with early distant metastasis. However, not all forms of the disease are aggressive and the identification of a biomarker that distinguishes patients with more aggressive disease from those with less aggressive disease would enable rational therapeutic choices. Here, we use the mathematical model to test whether the tumor-stroma interface morphology could be used as a biomarker to distinguish indolent from aggressive disease. Using a multicomponent mixture modeling framework, we identified a key model parameter that describes the stability of the tumor and the biological factors that influence proliferation and migration. We performed parametric analyses of this key model parameter, $\Lambda$, to ascertain its effect on gross morphology of the tumor. When the proliferation rate is slower than the migration rate (i.e., a low $\Lambda$), then the model predicts that the cancer cell clusters will intermingle with the stroma, resulting in an indistinct interface for the tumor and generating what have been described as “low mode” instabilities. Conversely, when the proliferation rate is higher than the migration rate (i.e., a high $\Lambda$), the model predicts that the tumor cells will grow with a distinct interface, as proliferation overcomes any attempts of isolated migrating cells to separate from and leave the main tumor bulk. We then use measurements of pathologic specimens to estimate the stability parameter in the model. For example, the stromal content can be inversely correlated with cell proliferation rates and the ratio of membrane axis ratios of cancer cells can be related to migration rates. Using an estimated value of the stability parameter, we find that the mathematical model is consistent with clinical observations and predicts that aggressive tumors would have a distinct interface between tumor and parenchyma with less stroma, whereas indolent tumors would not have a distinct interface but would have more stroma.
METASTASES MIGHT BE THE RESULT OF INFLAMMATORY PROCESSES BY ADAPTED IMMUNE CELLS

Leili Shahriyari*
Mathematical Biosciences Institute, The Ohio State University, Columbus, OH, USA;
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ABSTRACT

By querying published data sets, I hypothesize that chronic inflammation leads to deficient immune system that forms tumors in sites of inflammation. In other words, the main drivers of some inflammatory tumors are defective immune cells, not epithelial cells. Epithelial cells are just the victims; mutations occur in epithelial cells due to high levels of inflammatory signals secreted from defective immune cells. Furthermore, I hypothesize that sites of inflammation are metastatic sites, and some metastases are the result of inflammatory processes caused by defective immune cells at sites of inflammation rather than migration of tumor cells from one site to another site.
PERTURBATION OF SYSTEMIC TUMOR-IMMUNE DYNAMICS IN METASTATIC CANCER

Rachel Walker* and Heiko Enderling, Integrated Mathematical Oncology, Moffitt Cancer Center, Tampa, FL, USA; E-mails: rachel.walker@moffitt.org; Heiko.Enderling@moffitt.org

Jan Poleszczuk, Polish Academy of Sciences, Warsaw, Poland; E-mail: jan.poleszczuk@moffitt.org

ABSTRACT

Despite decades of effort, most disseminated cancers remain incurable, and progression from localized to metastatic disease is largely responsible for cancer-related mortality. In metastatic disease, an ongoing battle between tumor and host occurs at each site; tumor-associated antigens, stress proteins, and danger-associated molecular patterns can both initiate and continually stimulate an immune response against a tumor. Adding an additional layer of complexity, locally activated cytotoxic T cells traffic through the host circulatory system to also surveil metastasis elsewhere in the body. Thus, metastatic tumors are highly interdependent; changes in the nonlinear tumor-immune interactions in one tumor can perturb the systemic antitumor immune response, potentially facilitating spontaneous regression or aggressive outgrowth in distant sites. This can additionally influence the clinical outcome of therapeutic intervention, which depends on therapy-induced changes in tumor-immune dynamics both locally and systemically, as well as patient-specific initial conditions of the global disease.

Using the tools of mathematical oncology we gain insights into this complex interconnectivity between metastatic sites. ODE models have been developed which incorporate both local tumor-immune interactions in each tumor site and the trafficking of activated T cells systemically, and can be parameterized by experimental and clinical investigations. Using four primary tumor sites (lung, liver, breast, kidney) we simulate the growth behavior of a primary site upon both seeding, growth, and treatment of a secondary (or several) metastatic site(s).

In the presence of several metastatic sites, the dissemination of activated T cells is not necessarily intuitive and depends on many factors including the blood flow fraction to each organ and the tumor volume to organ size ratio. Certain sites may experience inhibition of growth, and other sites may be promoted upon seeding of an additional site. We computationally analyze all combinations of metastatic sites, and predict which sites are likely to benefit (tumor growth) and which to suffer (tumor shrinkage) in each combination based upon known properties of physiological blood flow and tumor volume at initial presentation. This allows the identification of which sites in each combination would be the optimal target for surgical therapy in order to induce the maximum reduction in overall tumor burden. Furthermore, we can simulate local radiation at each respective site, quantifying the difference in model-predicted decrease in overall tumor burden between individual targets. The results facilitate an improved understanding of general disease kinetics in the metastatic setting, emphasize that "local" therapy is highly likely to have systemic effects, and support the case for a paradigm shift in treatment target selection for metastatic disease.
MODELLING CANCER SPREAD WITH NON-LOCAL BIRTH-JUMP PROCESSES

Thomas Hillen*, Department of Mathematical and Statistical Sciences, University of Alberta, Edmonton, Canada; E-mail: thillen@ualberta.ca

ABSTRACT

The local spread of cancer is often well described by reaction-diffusion type of models. However, long range invasion such as metastasis cannot be described by these models. In this talk I will introduce a new class of models called “birth-jump processes”. These models allow for a systematic modelling of long-range invasion. The model is particularly useful if applied to cancer stem cells. I will present results on the tumor growth paradox and on invasion speeds.
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 session brings together researchers working on in-vivo and transmission models for diseases. We aim to enhance interdisciplinary understanding and collaborations across mathematics and biology. Further we bring in people from a variety of geographical locations with modeling experience relevant to local problems. This is part II of a two part mini-symposium.
Schedule:

- *Methicillin-Resistant Staphalococcus Aureus dynamics with Injection Drug Users*
  Rebekah Wagner, Folashade Agusto
  3:00 - 3:30

- *Transmission and Control of Multi Strain Influenza*
  Adnan A Khan*, Mudassar Imran
  3:30 - 4:00

- *Unexpected infection spikes in a model of Respiratory Syncytial Virus vaccination*
  Robert Smith*, Alexandra Hogan, Geoff Mercer
  4:00 - 4:30

- *Exogenous Re-infection Does Not Always Cause Backward Bifurcation in TB Transmission Dynamics*
  Oluwaseun Y. Sharomi
  4:30 - 5:00
Title: Methicillin-Resistant Staphylococcus Aureus dynamics with Injection Drug Users
Authors: Rebekah Wagner and Folashade Agusto (speaker, email: fbagusto@ku.edu)
Department of Ecology and Evolutionary Biology, University of Kansas, Lawrence KS, USA.

Abstract
A deterministic model for methicillin-resistant staphylococcus aureus (MRSA) with injection drug users is developed and presented. 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. Disease prevalence data from 2008-2013 was obtained for the non-IDUs from the Agency for Healthcare and Research and Quality (AHRQ). The data was fitted to a reduced MRSA transmission model involving only non-IDUs and the parameter estimates obtained was projected to the parameters for the low-and high-risk IDUs subgroups using risk factors obtained by constructing an ethogram. Sensitivity analysis was carried out to determine the parameters with the greatest impact on the reproduction number using the reduced model for the non-IDUs; the transmission probability and recovery rates for the subgroup was found to have the highest impact on the reduced model reproduction number.

Using the full MRSA transmission model, change in risky behaviors is studied via the vertical downward and upward movements among non-IDUs and low-and high-risk IDUs; more MRSA cases were found with increase in risky behaviors. However, when more IDUs enter rehabilitation programs (such as intervention, education, and clean needle exchange programs), there was a reduction in the number of MRSA cases in the community. The horizontal disease translation within the subgroups was also studied by implementing three different control strategies: low-effectiveness strategy, moderate-effectiveness strategy, and high-effectiveness strategy. Both moderate- and high-effectiveness control strategies were found to be effective in curtailing MRSA burden in the community; however, the high-effectiveness is a more effective control strategy.
Title: Transmission and Control of Multi Strain Influenza

Author: Adnan A Khan* (adnan.khan@lums.edu.pk), Mudassar Imran and Mohsin Ali

Affiliation: Department of Mathematics, Lahore University of Management Sciences

We first given an overview of some stochastic and deterministic models for the transmission dynamics of Influenza. We then present a deterministic model for the transmission when two strains are present. In particular, our model takes into account the effects of cross-immunity. Dynamical Systems analysis of the model is performed and conditions are obtained for the stability of the disease free state. We also show that if the DFE is unstable, the endemic state is persistent. Moreover the model undergoes competitive exclusion where Strain $j$ drives out Strain $i, (i = 1,2)$ to extinction under certain conditions. Finally we evaluate the efficacy of hospitalization as a control measure for the disease.
Unexpected Infection Spikes in a Model of Respiratory Syncytial Virus Vaccination
Robert Smith*, Alexandra B. Hogan and Geoffrey N. Mercer

Respiratory Syncytial Virus (RSV) is an acute respiratory infection that infects millions of children and infants worldwide. Recent research has shown promise for the development of a vaccine, with a range of vaccine types now in clinical trials or preclinical development. We extend an existing mathematical model with seasonal transmission to include vaccination. We model vaccination both as a continuous process, applying the vaccine during pregnancy, and as a discrete one, using impulsive differential equations, applying pulse vaccination. We develop conditions for the stability of the disease-free equilibrium and show that this equilibrium can be destabilised under certain extreme conditions, even with 100% coverage using an (unrealistic) vaccine. Using impulsive differential equations and introducing a new quantity, the impulsive reproduction number, we showed that eradication could be achieved with 75% coverage, while 50% coverage resulted in low-level oscillations. A vaccine that targets RSV infection has the potential to significantly reduce the overall prevalence of the disease, but appropriate coverage is critical.
 modelos para la dinámica de transmisión del Mycobacterium tuberculosis (TB) que incorporan reinfección exógena son conocidos para inducir el fenómeno de bifurcación retrógrada, un fenómeno dinámico asociado con la existencia de dos atraíbles estables cuando el número de reproducción del modelo es menor que la unidad. Este estudio muestra, por medio de un ejemplo contrario, que la reinfección exógena no siempre causa bifurcación retrógrada en la dinámica de transmisión del TB. En particular, se muestra que es la transmisibilidad de los individuos reinfecados, y no solo el proceso de reinfección, lo que causa el fenómeno de bifurcación retrógrada. Cuando los individuos reinfecados no transmiten infección, el equilibrio de enfermedad libre del modelo se muestra que es globalmente-asintóticamente estable (GAS) cuando el número de reproducción asociado es menor que la unidad. El modelo tiene un único equilibrio endémico cuando el umbral de reproducción supera la unidad. Se muestra, utilizando una función de Lyapunov, que el único equilibrio endémico es GAS para el caso especial con mortalidad inducida por la enfermedad y no transmisión por individuos reinfecados. Se muestra que aún si los individuos reinfecados transmiten infección, la bifurcación retrógrada sólo ocurre si su transmisibilidad excede un cierto umbral. Análisis de sensibilidad, con respecto al umbral de bifurcación retrógrada derivado, muestran que el fenómeno de bifurcación retrógrada es más probable que ocurra si las tasas de reinfección y transmisibilidad de individuos reinfecados son suficientemente altas. Además, es probable que ocurra si la fracción de progresores lentos (a TB activa) se incrementa o si las tasas de tratamiento (de casos sintomáticos) y la mortalidad inducida por la enfermedad son aumentadas. Por otro lado, la bifurcación retrógrada es menos probable que ocurra para incrementos en las tasas de reactivación endógena de casos latentes TB.
This minisymposium concerns the processes by which molecular motor proteins enable transport of mRNA and organelles in cells and tubulin along eukaryotic flagella. Beyond their central role in cellular function, various neurodegenerative diseases are believed to be associated at least in part to dysfunction in transport processes governed by molecular motors in neurons. Experimental data in recent years is providing new insights into how molecular motors work as a system, interacting with each other, with actin and microtubule fibers, and with other mediating proteins. These experiments provide targets to challenge and refine theoretical models for molecular motors to represent more effects relevant for their \textit{in vivo} functioning. The speakers in this minisymposium will describe recent efforts in using theoretical and computational models to explore the cooperation and competition of molecular motors of various species in achieving physiological goals. One particular focus will be the change of functional state of the motor proteins through attachment and detachment from the cytoskeletal structure or their release from binding sites at the flagellar base.
Modeling of Molecular Motor Systems

Thursday, July 20, 3:00–5:00, Alpine Room

Schedule:

- **3D model of myosin Va transporting fluid vesicles through actin intersections**
  Sam Walcott*, Andrew T. Lombardo, Shane Nelson, M. Yusuf Ali, Kathleen Trybus, David M. Warshaw
  3:00 - 3:25

- **How 3D geometrical properties of cargo influence their switching at cytoskeletal intersections**
  Ambarish Kunwar*, Anjneya Takshak
  3:25 - 3:50

- **Modeling messenger RNA localization in Xenopus (frog) egg cells**
  Maria-Veronica Ciocanel*, Bjorn Sandstede, Kimberly Mowry
  3:50 - 4:15

- **Effective dynamics of multiple molecular motors**
  Joe Klobusicky*, Peter Kramer
  4:15 - 4:40

- **Doubly Stochastic Poisson Model of Flagellar Length Control**
  Paul Bressloff, Bhargav Karamched*
  4:40 - 5:00
3D model of myosin Va transporting fluid vesicles through actin intersections

Sam Walcott*1, Andrew T. Lombardo2, Shane Nelson2, M. Yusuf Ali2, Kathleen Trybus2 and David M. Warshaw2

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In a cell, teams of molecular motors transport cargo through a crowded cytoskeletal environment. To gain insight into this system, we used a combination of experiment, computation and theory to examine how a team of myosin Va motors navigates a lipid vesicle through an actin intersection in 3D.

In the computational model, 1) the vesicle and actin filaments are rigid, and non-specific interactions between the two are neglected; 2) motors are stiff springs connected to the vesicle via a compliant pivot; 3) the vesicle is ideally fluid, so unbound motors diffuse rapidly across its surface, and attached motors only experience forces normal to the vesicle’s surface; 4) motors attach to actin depending on the energy cost of binding; 5) a motor, when experiencing force, steps along or detaches from the actin filament depending on the component of force along the actin filament; 6) motors usually perform 36nm steps, but occasionally take a shorter step; 7) the vesicle is in mechanical equilibrium.

Monte-Carlo simulations of this model show: 1) motor teams move the vesicle along actin in a left-handed spiral because the motors’ occasional short step is less than the helical repeat distance of actin; 2) at most, three motors can be attached to actin, due to the geometry of the system and the mechanics of the motors. Our measurements of motor teams translocating a vesicle against force imposed by a laser trap support this prediction; and 3) a motor team moving along an actin filament, when presented with another actin filament oriented at 90 degrees to and spaced between 50 and 250 nm above the original actin filament, has a 33% probability of switching filaments, a 61% probability of remaining on the original filament and a 6% probability of detaching, consistent with our experimental measurements of 33%, 60% and 7%, respectively.
How 3D geometrical properties of cargo influence their switching at cytoskeletal intersections

Ambarish Kunwar* and Anjneya Takshak  
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Eukaryotic cells employ specialized proteins called molecular motors for transporting organelles and vesicles from one location to another in a regulated and directed manner. These molecular motor proteins often work collectively as a team while transporting cargos which vary greatly in their shape and sizes—from spherical Lysosomes, Vacuoles and Peroxisomes to ellipsoid Mitochondria and Chloroplast, from almost cylindrical Golgi Bodies and small Microtubules to irregular shaped rRNA molecules and viral proteins. These cargos often navigate through complex three dimensional cytoskeletal network consisting of many microtubules and actin filaments to reach their destination, as single filaments are not long enough to traverse the entire dimensions of the cell from source to destination. Thus, cargos have to switch from one filament to another at these intersections during their intracellular travel for effective cell navigation. However, it is still very poorly understood how 3D geometrical properties of the cargos influence switching from one filament to another. One of the main reason is that most existing models exclusively deal with such cargo-motor systems as point-line systems in which the cargo is assumed to be like a dimensionless point particle and MTs are considered as lines without any thickness. Here, we use mathematical and computational modeling to understand how cargo switching depends on the 3D geometrical properties of the cargo being transported by a team of motor proteins.
Modeling messenger RNA localization
in Xenopus (frog) egg cells

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Abstract:
Messenger RNA (mRNA) localization is essential during the early development of many organisms, including during development of frog egg cells into embryos. This accumulation of RNA at the cell periphery is not well understood, but is hypothesized to depend on diffusion, active transport and anchoring mechanisms. We test these proposed mechanisms using dynamical systems and stochastic models and analysis, informed by parameter estimation. These methods allow us to extract asymptotic quantities such as the effective velocity and diffusion of the mRNA for large time, and to conclude that bidirectional transport is necessary for localization. Numerical studies of localization with transport restricted to model microtubule structures provide further insights into an unexplored anchoring mechanism at the cell bottom.
Effective dynamics of multiple molecular motors

Joe Klobusicky* and Peter Kramer
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Abstract

The transport of cargo attached to multiple motors may be modeled as a system of stochastic differential equations. Motors may switch between attached and detached states, each of which having separate equations for determining motor positions. In this talk, we derive effective velocities and diffusions for such motor systems. This involves limit theorems taken from renewal theory and multiscale averaging techniques. Effective quantities from identical and nonidentical motor systems will be compared with direct simulations from SDEs.
Doubly Stochastic Poisson Model of Flagellar Length Control

We construct and analyze a stochastic model of eukaryotic flagellar length control. Flagella are microtubule-based structures that extend to about 10 μm from the cell and are surrounded by an extension of the plasma membrane. Flagellar length control is a particularly convenient system for studying organelle size regulation, since a flagellum can be treated as one-dimensional structure whose size is characterized by a single length variable. The length of a eukaryotic flagellum is important for proper cell motility, and a number of human diseases appear to be correlated with abnormal length flagella. Flagellar length control is mediated by intraflagellar transport particles (IFTs), which are large motor protein complexes within a flagellum that transport tubulin (the basic building block of microtubules) to the tip of the flagellum. The critical length of the flagellum is thus thought to be determined by the dynamical balance between length-dependent transport and assembly of microtubules and length-independent disassembly at the tip. In our model we assume that IFT particles are injected into a flagellum according to a Poisson process, with a rate that depends on a second stochastic process associated with the binding and unbinding of IFTs to sites at the base of the flagellum. The model is thus an example of a doubly stochastic Poisson process (DSPP). We use the theory of DSPPs to analyze the statistics of IFTs as a function of flagellar length.
MS37: Analysis of Environmental Effects in Mathematical Biology

SMB 2017 Mini-Symposium Proposal

Organizer: Olcay Akman, Mathematics, Illinois State University, oakman@ilstu.edu

Session Title: Analysis of Environmental Effects in Mathematical Biology

Summary:

Unquestionable impacts of climate change have become significant factors in ecology, biology, and medicine. Climate change is chiefly responsible for species distribution shifts in many parts of the world (Thuiller et al. 2005). There is ample evidence of the ecological impacts of climate change in wide-range of environments, from polar terrestrial to tropical marine environments (Walther et al. 2002). For instance, the rates of extinction and survival of species are increasingly affected by global warming. The change of environmental conditions influence the epidemiological dynamics of infectious diseases, affecting the susceptibility of populations and introduce additional complications in compartmental models. Integrated pest management systems too are directly affected from ever changing environmental conditions. Hence, models that accommodate these possible environmental conditions need to be constructed.

Currently little work has been done to implement environmental impact estimation in compartmental or age-structured models with stochastic components. The additional stochasticity that the climate change introduces to these commonly employed models have not been quantified. With this session, we are aiming to introduce a fresh look at modifying the traditional models to incorporate the impact of environmental conditions.

With our minisymposium, we will examine models to estimate long-term population structure of plants, infectious disease modeling with unobserved population heterogeneity, integrated pest management systems under varying environmental conditions, and modeling long-term marine ecology.

The intended audience of our talks is researchers in marine, agricultural, and plant ecology and epidemiology.

Speakers, affiliations, tentative titles, (each talk is allocated 25 minutes):

Dan Hrozencik, Chicago State University, Plant population prediction via Leslie Matrices
Olcay Akman, Illinois State University, Frailty and environmental effect in compartmental models
James Peirce, University of Wisconsin La Crosse, River ecology prediction under El Nino, La Nina years
Timothy Comar, Benedictine University, Integrated pest management under irregular climate changes
Schedule:

- *Plant population prediction via Leslie Matrices*
  Dan Hrozencik*, Olcay Akman
  3:00 - 3:30

- *Frailty and environmental effect in compartmental models*
  Olcay Akman*, Timothy D. Comar*, Dan Hrozencik
  3:30 - 4:00

- *River ecology prediction under El Nino, La Nina years*
  James Peirce*, Olcay Akman, Aboubacar Seck
  4:00 - 4:30

- *Integrated pest management under irregular climate changes*
  Timothy D. Comar*, Olcay Akman, Dan Hrozencik
  4:30 - 5:00
PLANT POPULATION PREDICTION VIA LESLIE MATRICES

Dan Hrozencik*, Chicago State University, dhro@att.net
Olcay Akman, Illinois State University, oakman@ilstu.edu

Abstract

Rare flowering North American plants are of particular concern to conservation biologists interested in preserving species diversity. The impact (both short-term and long-term) of increasingly fluctuating environmental conditions on the demographic health of rare plants is not completely understood. In particular, rare plants are very likely more sensitive to fluctuating environmental conditions than more abundant species. In this talk we investigate whether a rare species Eupatorium reinosum is more adversely affected by environmental stochasticity than a common species, Eupatorium perfoliatum. We use empirical data to construct stochastic Leslie matrices to compare different populations within each species. The stochastic Leslie matrices are then used to determine population dynamics and predict population growth.
ENVIRONMENTAL EFFECT ESTIMATION UNDER HIDDEN HETEROGENEITY

Olcay Akman*, Illinois State University, oakman@ilstu.edu
Timothy D. Comar*, Benedictine University, tcomar@ben.edu
Dan Hrozencik, Chicago State University, dhro@att.net

Abstract

Most epidemic related models that involve lifetime estimation or ecological models used to predict survival rates assume that the members of the population in question are affected from the environment identically. However it is not unreasonable to assume that the environmental effect on certain individuals vary due to their frailty. The concept of frailty provides a suitable way to introduce random effects in the model to account for the unobserved heterogeneity of the population. In its simplest form, a frailty is an unobserved random factor that modifies the lifetime of an individual or a group or cluster of individuals. In this talk we will explore extending commonly used models to accommodate the frailty component due to environmental effects.
MODELING THE INFLUENCE OF EL NIÑO ON PARASITE TRANSMISSION IN SAND CRAB POPULATIONS AND SHOREBIRD ABUNDANCE ALONG THE CALIFORNIA COAST

James Peirce*, University of Wisconsin La Crosse, jpeirce@uwlaex.edu
Olcay Akman, Illinois State University, oakman@ilstu.edu
Aboubacar Seck, Illinois State University, aseck@ilstu.edu

Abstract

Pacific mole crabs (*Emerita analoga*) are one of the most important and abundant invertebrates in sandy beach environments. Consequently, they are a common food source for shorebirds and sea otters. Since the mole crab serves as the primary intermediate host for acanthocephalans parasites, they have been linked to a number of mortality events. It is currently estimated that 13-16% of deaths in the threatened California sea otter population have been caused by infection. In addition, unusually high loads of acanthocephalan parasites have been linked to episodic deaths of thousands of surf scoters. Studies suggest that acanthocephalan development and transmission may be strongly effected by weather patterns. In this presentation we will introduce a system of differential equations for parasite transmission between scoter, crab, and sea otter populations. Temperature-dependent parameters within the model allow us to examine the role climate oscillation in El Niño and La Niña years has on abundances of infected hosts.
MODEL SELECTION AND PERMANENCE IN A STOCHASTIC INTEGRATED PEST MANAGEMENT MODEL

Timothy D. Comar*, Benedictine University, tcomar@ben.edu
Olcay Akman, Illinois State University, oakman@ilstu.edu
Dan Hrozencik, Chicago State University, dhro@att.net

Abstract
We present a model for integrated pest management with stochastic and mixture model components to create further flexibility in modeling the impacts of random environmental changes on an integrated pest management system. In particular, we first determine the conditions under which solutions of our deterministic mixture model are permanent. We then analyze the stochastic model to find the optimal value of the mixing parameter that minimizes the variance in the efficacy of the pesticide. Additionally we perform a sensitivity analysis to show that the corresponding pesticide efficacy determined by this optimization technique is indeed robust. Through numerical simulations we show that permanence can be preserved in our stochastic model. Our study of stochastic version of the model indicates that our results on the deterministic model provide informative conclusions about the behavior of the stochastic model.
MS38: Confronting Biological Models with Data: Dealing with Complexity and Sparsity II

Minisymposium Title: Confronting Biological Models with Data: Dealing with Complexity and Sparsity II  
Organizer: Noelle G. Beckman, nbeckman@sesync.org 
Co-Organizer: Richard Schugart, richard.schugart@wku.edu

Summary: Models range from strategic models that require large amounts of data to parameterize for prediction to tactical models that require less data but are poorer at extrapolating beyond the range of the data as they are conceptually simpler. With advances in environmental sensors, imaging, remote sensing, and coordinated efforts to curate data in publicly accessible repositories, the quantity of data is rapidly increasing in the environmental and health sciences. However, as data increases into the realm of big data, mathematical and statistical challenges arise to integrate these data with mathematical models for better understanding and prediction. Challenges in effectively synthesizing data with mathematical models include simplifying often complex data with minimal loss of information and handling sparsity in data as the size and complexity of data increases. As data from experimental and observational studies can inform the development of models, models can be used to inform data collection. In this second session, speakers will present a variety of mathematical and statistical advances in merging different types of data with models for understanding and prediction in ecology and ecosystem health.
Schedule:

- **Analyzing data using dynamical systems models: Modern approaches and challenges**
  Paul Hurtado*, Jace Gilbert
  3:00 - 3:20

- **Initial abundance and stochasticity influence competitive outcome in experimental communities**
  Tad Dallas*, Brett Melbourne, Geoff Legault, Alan Hastings
  3:20 - 3:40

- **Assessing species’ risk under climate change**
  Noelle G. Beckman*, Roberto Salguero-Gomez, Thomas Cornulier, James Bullock
  3:40 - 4:00

- **The Great Canadian Worm Invasion; Invasive Species and Approximate Bayesian Computing**
  Oksana A. Chkrebtii, Erin K. Cameron, David A. Campbell*, Erin M. Bayne
  4:00 - 4:20

- **Hidden Markov models to predict mountain pine beetle eruption**
  Dean Koch*, Mark Lewis, Subhash Lele
  4:20 - 4:40
Authors:
Dr. Paul Hurtado*, Department of Mathematics and Statistics, University of Nevada, Reno, 
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Jace Gilbert, Department of Mathematics and Statistics, University of Nevada, Reno, 
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Title: Analyzing data using dynamical systems models: Modern approaches and challenges

Abstract: In this talk, I will provide an introduction to using dynamic models (ODEs) as statistical models, and to some tools and approaches for overcoming mathematical and statistical challenges that can arise in applications. I will illustrate different uses of dynamic models as statistical models using multiple ecological examples, using both empirical and synthetic (simulated) data. I will present different methods for parameter estimation and uncertainty analysis, including our recent work on integrating bifurcation information into some of these methods, and how these can be used in conjunction with an assessment of a model’s statistical properties to inform experimental design or data collection protocols. I will conclude the talk by briefly mentioning how our current toolset might benefit from future research.
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Alan Hastings, Department of Environmental Science and Policy, University of California-Davis, Davis, CA, USA, amhastings@ucdavis.edu

Title: Initial abundance and stochasticity influence competitive outcome in experimental communities

Abstract: Stochasticity influences single species population dynamics, typically elevating extinction risk. On the other hand, stochasticity can also allow for multi-species coexistence when competition would otherwise lead to exclusion. However, many forms of stochasticity exist, and there is currently no consensus on how each form of stochasticity may influence competitive outcome. In many cases, stochasticity can cause competitive indeterminacy, in which the outcome of competition varies in replicate communities. Here, we examine the role of stochasticity on competitive indeterminacy and extinction risk by extending a set of eight stochastic Ricker models incorporating combinations of four distinct forms of stochasticity; environmental stochasticity, demographic stochasticity, demographic heterogeneity, and stochastic sex determination. Using replicated populations of two Tribolium species, we competed the set of stochastic models, finding that demographic stochasticity, environmental stochasticity, and stochastic sex determination were the prominent causes of population variability. While the standard Poisson Ricker model incorporating demographic stochasticity does not allow for competitive indeterminacy or transient coexistence given fitness differences between competitors, our best fit model suggests that stochastic processes allow to transient coexistence and competitive indeterminacy. This probabilistic view of competitive outcome dependent on the initial abundance of competing species could explain the anomalous long term co-occurrence observed in previous Tribolium experiments at moderately long timescales. Further, the incorporation of the various stochastic forces into demographic models suggest that current estimates of extinction risk, coexistence, and biological invasion probabilities may be inaccurate when based on models only incorporating demographic stochasticity.
Title: Assessing species' risk under climate change

Abstract: Global change affects the ecology and evolution of dispersal, limiting the ability of species to move or adapt to global change events. Due to the long-term and spatially-complex dynamics of plant populations, understanding and predicting their responses to global change is empirically and mathematically challenging. We apply recent advances in the study of species’ movement and develop a general classification scheme to assess the risk of plant extinction in response to climate change in continuous landscapes. Using a Bayesian approach, we synthesize existing data on dispersal, functional traits, and demography to generate virtual species with realistic dispersal kernels and life-history strategies. We sample these virtual species to parameterize integrodifference equations and approximate population spread in continuous landscapes. Using this approach, we obtain predictors of risk that are related to easily measurable functional traits that will inform the types of species least likely to track a shifting climate. In future research, this approach will be extended to predict extinction risk of plant species in fragmented landscapes. This research will help identify species at greatest risk and aid the development of conservation strategies to ensure their persistence under global change.
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Erin M. Bayne, Department of Biosciences, University of Alberta, bayne@ualberta.ca

Title: The Great Canadian Worm Invasion; Invasive Species and Approximate Bayesian Computing

Abstract: After being brought in by pioneers for agricultural reasons, European earthworms have been taking North America by storm and are starting to change the Alberta Boreal forests. This talk uses an invasive species model to the rate of new worm introductions and how quickly they spread with the goal of predicting the future extent of the great Canadian worm invasion. To estimate the introduction and spread rates we need to deal with an unknown number of introductions, which in turn results in an unknown number of model parameters. The complexity of the model means that we need to turn to Approximate Bayesian Computation methods. Approximate Bayesian Computation is a step in the right direction when it's just not possible to actually do the right thing- in this case using the exact invasive species model is infeasible.
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Prof. Subhash Lele, Department of Mathematical and Statistical Sciences, University of Alberta, slele@ualberta.ca

Title: Hidden Markov models to predict mountain pine beetle eruption

Abstract: In recent years, large areas of lodgepole pine forest in Western North America have been disturbed by a series of severe and widespread outbreaks of a native insect, the mountain pine beetle (Dendroctonus ponderosae). The dramatic and unprecedented consequences of this epidemic on forest ecosystem services have motivated many researchers to investigate the causes and dynamics of pine beetle outbreaks. For decades now, government officials in British Columbia (BC) have been using remote sensing to acquire spatially referenced data on pine mortality and associated environmental covariates. With yearly data spanning 2000-2017 at a resolution of 1 km$^2$ and a spatial extent of nearly 1 million km$^2$, this ecological time series is unusually large and complete. How can we connect such a massively detailed dataset with nonlinear population models? In this talk I will explain how spatial statistical techniques can be used to tackle this modelling problem. The core model combines a novel formulation of nonlinear discrete-time growth and dispersal patterns for eruptive forest pests with a stochastic component capturing the environmental noise shared by nearby pine stands. Because of the high-dimensionality, traditional maximum likelihood based inference can be computationally infeasible. I will discuss techniques for speeding up computations of the likelihood function, as well as pseudolikelihood-based alternatives. I will also discuss the model’s potential for regional planning of future pine beetle control efforts in BC.
Recent studies have emphasized the role of phenotypic plasticity – ability of genetically identical cells to alter their phenotypes in response to many signals – as a significant clinical challenge to treating solid tumors. Tumor cells utilize this plasticity to evade therapies, metastasize, colonize, and thereby to accelerate tumor evolution. This plasticity can manifest in many forms and across cancer types, and our different speakers in the minisymposium have tackled this challenge via different mathematical modeling approaches closely integrated with relevant experimental data. Discussions at the minisymposium for these different attempts will benefit one another and can lead to further robust multi-scale spatiotemporal models quantifying tumor plasticity and evolution.

Moreover, our minisymposium aims to foster a strong community of quantitative oncologists, synergistically drive a better understanding of tumor heterogeneity, and aid in guiding optimal treatment modalities and in improving prognostic risk.

Here are our details:
Organizer: Mohit Kumar Jolly (mj21@rice.edu)
Co-organizer: Philipp Altrock (philipp.altrock@moffitt.org)
Schedule:

- *Stromal plasticity in bone metastasis*
  Etienne Baratchart*, ChenHao Lo, Conor C. Lynch, David Basanta
  3:00 - 3:30

- *Decoding Cell Identity from Models of Transcription Factor Networks*
  Vito Quaranta
  3:30 - 4:00

- *Network-based Dynamic Modeling and Control Strategies in Complex Diseases*
  Jorge G. T. Zañudo*, Réka Albert
  4:00 - 4:30

- *Quantifying epithelial-mesenchymal plasticity during cancer progression*
  Mohit Kumar Jolly, Jason T George, Dongya Jia, Satyendra C Tripathi, Samir M Hanash, Herbert Levine
  4:30 - 5:00
Stromal plasticity in bone metastasis

Etienne Baratchart¹, ChenHao Lo¹, Conor C. Lynch¹, David Basanta¹

¹Moffitt Cancer Center, Tampa, FL
Email: david.basanta@moffitt.org

Phenotypic plasticity plays an important but not fully recognized role in driving somatic evolution. This plasticity is relevant not only in the tumor cells but maybe specially so in other cells within the tumor microenvironment. In bone metastatic prostate cancer there are a number of stromal cells whose plasticity could play a key role in driving the success of the metastasis. A good example are macrophages, cells that derive from the same lineage as osteoclasts (in charge of bone remodeling), are part of the innate immune system and are responsible for both pro-inflammatory and anti-inflammatory behaviors. Their plasticity is highly dynamic and controlled by the interactions with other cells. The signals they exchange orchestrate bone homeostasis, remodeling and fracture healing. This flexibility allows macrophages to cope with many scenarios, including the phagocytosis of tumor cells, but also means that they could (and often are) co-opted by the tumor to support its growth. We have developed a mathematical model that describes the different cellular populations in the bone with a special emphasis on the macrophage population. We calibrated this model with data from in vivo experiments from normal bone response to fracture and remodeling and used it to investigate how prostate cancer metastases could interact and co-opt them in order to sustain their growth.
Decoding Cell Identity from Models of Transcription Factor Networks

Vito Quaranta*, MD  
Director, Quantitative Systems Biology Center  
Professor, Department of Cancer Biology  
Vanderbilt University School of Medicine  
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The definition of epigenetic mechanisms that maintain the differentiated state of a cell has become a critical problem in this post-genomic era. Starting from bioinformatics analyses of large gene expression datasets, we specify the biochemical identity of a cell as a set of co-expressed gene modules. From these modules, we derive the corresponding network of transcription factors (TFs) that ultimately specify cell identity. The topology of TF networks is derived from databases and literature on TF interactions. After further curation based on prior knowledge, we simulate TF network dynamics using logic-based mathematical modeling. Biologically, predicted network attractors represent possible alternative differentiation states supported by a core TF network, which can then be validated experimentally. We propose that with this workflow it is possible to predict single-cell state transitions in a cell population subjected to perturbations. We show examples of the usefulness of this approach in identifying cancer cell drug-sensitive or –resistant states.
Network-based Dynamic Modeling and Control Strategies in Complex Diseases

Jorge G. T. Zañudo¹,²,³ and Réka Albert¹,⁴

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In order to understand how the interactions of molecular components inside cells give rise to cellular function, creating models that incorporate the current biological knowledge while also making testable predictions that guide experimental work is of utmost importance. To model the dynamics of the networks underlying complex diseases we use network-based models with discrete dynamics, which have been shown to reproduce the qualitative dynamics of a multitude of cellular systems while requiring only the combinatorial nature of the interactions and qualitative information on the desired/undesired states. Here I present some recently developed analytical and computational methods for analyzing network-based models with discrete dynamics. The methods presented are based on a type of function-dependent subnetwork that stabilizes in a steady state regardless of the state of the rest of the network, and which we termed stable motif. Based on the concept of stable motif, we proposed a control method that identifies targets whose manipulation ensures the convergence of the model towards a dynamical attractor of interest (which are identifiable with the cell fates and cell behaviors of modeled organisms). We illustrate the potential of these methods by collaborating with wet-lab cancer biologists to construct and analyze a model for a process involved in the spread of cancer cells (epithelial-mesenchymal transition). These methods allowed us to identify the subnetworks responsible for the disease and the healthy cell states, and show that stabilizing the activity of a few select components can drive the cell towards a desired fate or away from an undesired fate, the validity of which is supported by experimental work.
Quantifying epithelial-mesenchymal plasticity during cancer progression

Mohit Kumar Jolly\textsuperscript{1}, Jason T George\textsuperscript{1}, Dongya Jia\textsuperscript{1}, Satyendra C Tripathi\textsuperscript{2}, Samir M Hanash\textsuperscript{2}, Herbert Levine\textsuperscript{1}

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Epithelial-to-Mesenchymal Transition (EMT) and its reverse Mesenchymal-to-Epithelial Transition (MET) often play crucial roles in cancer metastasis and drug resistance. Recent reports highlight that EMT and MET are not ‘all-or-none’ processes, instead cells can attain a hybrid epithelial/mesenchymal (E/M) phenotype. But, a hybrid E/M phenotype has been tacitly assumed to be ‘metastable’ that can be attained only transiently \textit{en route} to EMT/MET, and remains poorly characterized. Rapid progress in mapping the regulatory networks for EMT/MET has enabled developing computational systems biology models to characterize a hybrid E/M phenotype. Here, using mechanism-based mathematical modeling, we identify a set of ‘phenotypic stability factors’ (PSFs) – OVOL2 and GRHL2 – that can help maintain cells in a hybrid E/M state. Next, we identify H1975 cells as stably maintaining a hybrid E/M state over multiple passages, and validate the role of these PSFs experimentally. We show that the knockdown of these PSFs that act as a ‘brake’ on full EMT drives cells to a fully mesenchymal phenotype. Finally, we devise a statistical model built upon gene expression profiles that can quantitatively predict where a given sample lies on a scale of 0 (fully epithelial) to 2 (fully mesenchymal). Intriguingly, GRHL2 and OVOL2 were identified among the top predictors that could resolve a hybrid E/M phenotype, through an unsupervised screening, thereby reinforcing their suggested roles as PSFs. This model can recapitulate the experimentally observed behavior for multiple scenarios such as EMT induction, and unravels the association of a hybrid E/M phenotype with poor clinical outcomes across multiple tumor types. Collectively, our integrated theoretical-experimental approach enables a quantitative understanding of the role of a hybrid E/M state in tumor progression, and reinforces the emerging notion that cells in a hybrid E/M state may be more aggressive than cells in a full EMT state.
Quantifying phenotypic plasticity in cancer cells

Poster Session

Monday, July 17
6:30–8:00
Natural History Museum of Utah

List of Groups
Group 1: Bacteria, Biochemistry and Biophysics
Group 2: Cancer
Group 3: Cell Biology
Group 4: Computational Biology
Group 5: Dynamical Systems
Group 6: Ecology and Evolution
Group 7: Education
Group 8: Epidemiology
Group 9: Fluids and Physiology
Group 10: Immunology, Pharmacology and Systems Biology
A. – Manu Aggarwal (Presenter)
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   – Dr. Nick Cogan
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B. – Title: Bacterial biofilm formation: Experiment, Model and Sensitivity Analysis

   – Abstract: *Xylella fastidiosa*(Xf) is a nutritionally fastidious xylem-limited bacterial plant-pathogen which has been associated with various diseases like Pierce’s disease, leaf scorching, citrus variegated chlorosis and olive quick decline syndrome. It is believed that the biofilm formation by the bacteria plays an important role in both causing diseases in the infected plant and the spread of infection to the neighboring plant population by vector-transmission. It is hypothesized that metal ions like Zinc can be used to impact Xf biofilms. This report develops and explores a population-model for batch culture experiments under different Zinc concentrations. The changes in the behavior of the model with respect to Sobol Indices are also analyzed under the different experimental conditions.
List of authors:

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**Title:**  
Bacterial Persistence, Mathematical Modeling, Experimental Validation and Parameter Estimation

**Abstract:**  
Bacterial infections cause many chronic diseases such as tuberculosis, meningitis and pneumonia. These diseases may not respond to treatment with antibiotics. Bacteria evade antibiotics using a variety of tolerance mechanisms such as modifying their genotypic or phenotypic expression. They can also protect themselves in structured communities referred to as biofilms. In order to outsmart the bacteria we must have a better understanding of these tolerance mechanisms. The focus of this study is on the dynamics between phenotypes. Understanding the changes in the persistent bacterial population before and after antibiotic challenge is of primary importance for creating treatment methods. In this research we intend to bridge the gap between experimental and theoretical/mathematical models and to deliver brighter intuitions to experiments that describe several current hypotheses regarding phenotypic expression. Finding the best applicable set up to eliminate the bacteria by comparing our theoretical model against experimental data, is our
SMB 2017 Poster Abstract

Generalized theory on the mechanism of DNA renaturation: Stochastic Nucleation and Zipping

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Abstract:
Renaturation (or hybridization) of complementary single strands of DNA is an important phenomenon in molecular biology and biological physics. Understanding the kinetic mechanism of renaturation is very useful to further understand the unwinding-rewinding dynamics of double stranded DNA under both in vitro and in vivo conditions. We have developed a stochastic dynamics based model on the DNA renaturation phenomenon to explain various scaling behaviours of renaturation rate. According to our model there are at least three steps in the renaturation process viz. Non-specific contact formation, correct-contact formation and nucleation, and zipping. It seems that the square-root dependency of the overall renaturation rate constant on the length of reacting single strands originates mainly from the geometric constraints in the diffusion controlled non-specific contact formation step. On the other hand the inverse scaling of the renaturation rate with the sequence complexity originates from the stochastic zipping which involves several rounds of crossing of free-energy barrier at microscopic level. When the sequence of denaturing single strands of DNA is repetitive with less complexity then the cooperative effects will not be noticeable since the parallel zipping will be a dominating enhancement factor. However for DNA strand with high sequence complexity and length, one needs to consider the cooperative effects both at microscopic and macroscopic levels to explain various scaling and kinetic behaviours of the overall renaturation rate.

Keywords: Stochastic dynamical process, unwinding and rewinding of DNA, diffusion controlled reactions.
SMB 2017 Poster Abstract

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B.

Title: Residue interaction network metrics suggest commonalities among amyloidogenic proteins

Abstract: Several human diseases such as Alzheimer's disease are thought to be partly caused by aggregating proteins and peptides called amyloids. Amyloidogenic proteins have little sequence and 3-dimensional structural similarity. To find commonalities among amyloidogenic proteins, PDB files were used to create residue interaction networks using the Protein Graph Repository Converter. Cytoscape was used to determine network metrics, and the amyloids were compared to random controls and real protein controls. Several measures were statistically different from controls. By comparing wild type to amyloidogenic variants of lysozyme and beta-2-microglobulin, we conclude that proteins with alpha class characteristics may follow the identified trends more closely than all-beta class proteins. Furthermore, stress metrics identify amino acid residues important for overall structure that other experimental studies have determined to be important for oligomerization. Understanding the commonalities among amyloidogenic proteins may be a step toward discovering treatments for these diseases.
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B. Title And Abstract
Title: Transport of Particles in a Biofilm-lined Hot Spring Effluent Channel
Abstract: Communities of bacteria adhering to surfaces--biofilms--are commonly found in natural and industrial systems, including hot spring effluent channels under flow conditions. Modeling biofilms in the context of channel flow is important in understanding many natural systems. We develop a model which addresses the rate at which cells move in or out of the flow in a natural hot spring drainage channel. This is done by building a two-dimensional partial differential equation model of the stream. The model is parameterized using data gathered at Mushroom Spring in Yellowstone National Park. Using this data, we calculate erosion and adhesion rates at steady state in both upper and lower regions of the stream.
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B. Title and Abstract

BioSimulator.jl: Stochastic Simulation in Julia

Biological systems with multiple overlapping feedback and feedforward loops are often inherently stochastic. Furthermore, many systems are analytically intractable, and dynamical predictions based on deterministic models can be grossly misleading. Stochastic simulation algorithms based on continuous-time Markov chains allow researchers to generate accurate time-evolution trajectories, test the sensitivity of models to key parameters, and quantify frequencies of rare events. Situations where stochastic simulation is especially helpful involve: a) rare events such as extinction and mutation, b) key molecules present in small numbers, c) rare reactions with dramatic influence on the dynamics of the system, and d) population cycles arising from demographic stochasticity. Examples of such systems include gene expression networks, tumor suppressor pathways, and demographic and ecological systems. We present BioSimulator.jl (https://github.com/alanderos91/BioSimulator.jl), implemented in Julia, which aims to provide investigators with a tool that enables 1) quick and intuitive model prototyping, 2) efficient simulation, 3) visualization of simulation output, and 4) implementing new stochastic simulation algorithms. The fast performance and expressive syntax of Julia allow BioSimulator.jl to deliver promising results without glue code bridging multiple modules across different languages. As the Julia language matures, we hope to incorporate spatial effects into BioSimulator.jl and extend the software to interesting applications in biological systems.
Group 2: Cancer

Authors: Johnna P. Barnaby (presenter) and Harsh V. Jain

Title: Quantifying the Immune Response Emanating from Prostate Cancer Treatments

Abstract: Prostate Cancer (CaP) is a public health concern because of its high recurrence rate. Initially CaP is treated with androgen deprivation therapy (ADT), resulting in an increased immune response at the cancer site. However, ADT fails to treat recurring tumors, and immunotherapies are being used to target the tumors. New evidence points to using a combination of these two treatments. We will investigate this using a mathematical model that includes temporal dynamics of key cells and chemokines, and drug action.
Characterisation of Macrophage Infiltration into Solid Tumours

SMB 2017 Poster Abstract

Joshua A. Bull (bull@maths.ox.ac.uk, presenter)1, Prof. Sarah Waters (waters@maths.ox.ac.uk)2, Prof. Vicente Gran (vicente.gran@eng.ox.ac.uk)3, Dr. Tom Quaiser (tom.quaiser@roche.com)4, Dr. Franziska Mech (franziska.mech@roche.com)4 and Prof. Helen Byrne (helenb@maths.ox.ac.uk)1

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Abstract

There is considerable interest in targeting tumour associated immune cells in order to reduce tumour progression [1, 3]. Growing tumours are infiltrated by a variety of immune cells including macrophages, a type of immune cell which can adopt a range of pro- or anti-tumour phenotypes depending on microenvironmental cues. The spatial distribution of macrophages within a tumour varies from patient to patient, between different tumour types, and is related to patient outcome.

Hypoxic tumour cells are a source of colony stimulating factor-1 (CSF-1), a cytokine which causes macrophages to express a pro-tumour phenotype by producing vascular growth factors. CSF-1 also acts as a key chemoattractant for macrophages, recruiting them to hypoxic areas. One hypothesis driving current pharmaceutical research is that tumour-associated macrophages (TAMs) which infiltrate deep into tumour areas express this pro-tumour phenotype. By manipulating the phenotype of TAMs, patient prognosis could be improved [1]. A key target for treatment is the CSF-1 receptor on the cell-surface of macrophages, and recent experimental results indicate that antibodies which block the CSF-1 receptor may prevent macrophages from expressing this pro-tumour phenotype and hence lead to tumour reduction [3].

To assess the potential of macrophage-targeting tumour treatments, we need to understand the mechanisms by which macrophages localize in solid tumours, and the processes that regulate their phenotype. This poster will introduce an agent-based multiscale model of macrophage infiltration into tumour spheroids in the presence of CSF-1, implemented in the CHASTE (Cancer, Heart and Soft Tissue Engine) framework [2]. We use this to investigate which aspects of tumour biology are important in controlling macrophage infiltration, including variations in chemotactic sensitivity and mechanical properties of the tumour such as the density of cells. We also use machine learning and a range of statistical techniques to quantify macrophage infiltration from histological imaging of surgically-removed tumours. This allows us to directly compare simulated and experimentally observed distributions, predict which tumours will respond well to macrophage-targeting therapies and how this response is regulated by the spatial distribution of macrophages within a tumour.

References

Differential dynamics of p53 in response to ionizing and ultraviolet radiation

Elizabeth Fedak (presenting), Dr. Fred Adler, Dr. Joshua Schiffman
March 31, 2017

1 Abstract

The tumor suppressor protein p53 is one of the most well-studied proteins in microbiology due to its role in regulating cell survival and apoptosis after stress. Recent advances, both in modeling and in single-cell experiments, have established the importance of p53 dynamics in the cellular stress response. We construct a model proposing a mechanistic explanation for two conflicting behaviors of p53: p53 oscillates at a low level in response to ionizing (IR) radiation; but increases proportionally, without oscillations, to ultraviolet (UV) radiation. Our work suggests that this difference in response is not only influenced by the speed at which DNA damage is detected and repaired, but may also require a stabilizing positive feedback loop activated by unphosphorylated p53. This process has implications for tumorigenesis and tumor survival for cancerous cells with gain-of-function p53 mutations.

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B. Title and Abstract
A tumor induced angiogenesis model calibrated with in vivo MRI data

The clinical care of patients with brain tumors is currently limited by standard radiographic measurements that fail to accurately evaluate or predict response to therapy. To address this limitation, we are developing biophysical models of tumor growth and response that can be initialized and calibrated by non-invasive imaging measurements to provide individualized tumor growth predictions. A critical component of solid tumor growth is the recruitment of new vessels to support tumor cell proliferation. The spatial variation of vasculature within the tumor also effects the development of regions of hypoxia and necrosis and may play a critical role in the efficacy of chemo- and radiotherapy. Accurate characterization of the tumor vascularization on an individual basis may provide more accurate assessments of tumor response and provide clinicians with a powerful tool to guide patient care. In this work, we develop and evaluate a novel model of tumor induced angiogenesis that can be initialized and calibrated on an individual basis.

To evaluate this model, rats (n = 4) with C6 gliomas were imaged with diffusion-weighted MRI (DW-MRI) and dynamic contrast enhanced MRI (DCE-MRI) seven times over 10 days. DCE-MRI data was used to identify tumor regions and estimate blood volume on a voxel basis. Cellularity was then estimated within tumor regions using DW-MRI data. We model the spatio-temporal evolution of blood volume (BV) that we assume to be proportional to endothelial cell density. Model parameters describing endothelial cell diffusion, proliferation, growth, regression, and chemotaxis were calibrated from the tumor cellularity and blood volume data. The overall model fit was assessed by using all available time points to calibrate the model, while the predictive accuracy of this model was assessed by calibrating the model to a subset of the time points. The agreement and correlation between the measured and modeled cerebral blood volume was assessed by the concordance and Pearson correlation coefficients (CCC and PCC, respectively).

The model estimated BV for all rats had a strong level of correlation and agreement with the measured data (PCC = 0.70, CCC = 0.56) for the model fit scenario. Lower correlation and agreement was observed for the prediction scenario (PCC = 0.62, CCC = 0.45). These preliminary results indicate the potential to accurately model tumor induced angiogenesis from clinically relevant imaging measurements. This model could be combined with existing biophysical models of tumor cell growth to spatially alter tumor cell proliferation or death (as a function of treatment or vessel collapse) to develop individual tumor “forecasts”.

We gratefully acknowledge the support of NCI U01 CA174706 and CPRIT RR160005.
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B. Title and Abstract:
A spatiotemporal model of breast cancer using patient specific MRI data

Clinical methods for assessing tumor response to neoadjuvant therapy are largely rudimentary, monitoring only temporal changes in tumor size. Our goal is to predict tumor response to neoadjuvant therapy in breast cancer using a mathematical model that uses non-invasive imaging data obtained from individual patients. Previously, a reaction-diffusion model coupled with logistic growth for breast cancer was shown to outperform clinically used measures for predicting tumor response to therapy when initialized with patient specific magnetic resonance imaging (MRI) data. Here we extend this model to include the effects of vascularization on tumor cell proliferation and drug delivery.

The model is 2D, initialized using patient specific diffusion weighted (DW-) MRI and dynamic contrast-enhanced (DCE-) MRI data—where size, shape, and cellularity across the entire tumor were calculated per scan slice. The parameters of the model, such as diffusion and proliferation values, were calibrated using the first two of four MRI scans (pre-treatment, after first treatment cycle, at midpoint of treatment, and after treatment completion) during the course of neoadjuvant therapy. The DCE-MRI data was used to identify spatiotemporal variations in tumor perfusion with the extended Tofts-Kety model. The derived MRI-based physiologic parameters were then used to model changes in tumor cell proliferation and delivery of therapy within the tumor. An additional calibration for the tumor cell carrying capacity was also calculated on a patient-specific basis. All model simulations were evaluated using the Crank-Nicolson finite difference scheme.

With the above modifications, preliminary results using a cohort of five patients with varying subtypes of breast cancer and associated therapeutic regimens show substantial reductions in the percent error between the model’s prediction and the experimentally-measured results for the third scan. Next steps include using the MRI data to incorporate drug-specific mechanisms for inducing cell death and temporally evolving the vasculature.

We acknowledge the support of U01 CA174706, U01 CA154602, and CPRIT RR160005.
Mathematical modeling of brain tumor abrogation by immunotherapy with T11 target structure

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&

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Abstract
T11 Target structure (T11TS), a membrane glycoprotein isolated from sheep erythrocytes, reverses the immune suppressed state of brain tumor induced animals by boosting the functional status of the immune cells. This study aims at aiding in the design of more efficacious brain tumor therapies with T11 target structure. We have developed a mathematical model for malignant gliomas or brain tumor and the immune system interactions by introducing the role of immunotherapeutic agent/drug T11TS. The model encompasses considerations of the interactive dynamics of malignant glioma cells, macrophages, cytotoxic T-lymphocytes (activated CD8+ T- cells), immune-suppressive factor TGF-β, immune-stimulatory factor IFN-γ and the T11TS. We have performed sensitivity analysis in order to determine which of the state variables are more sensitive to the given system parameters. The results of the proposed mathematical model are compared with experimental data procured from our collaborator Prof. Dr. Swapna Chaudhuri, School of Tropical Medicine, Kolkata, India. Computer simulations were used for model verification and validation, which underscore the importance of T11 target structure in brain tumor therapy.
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B: Title and abstract

‘The legacy of necrosis in tumour response to fractionated radiotherapy’

Current protocols for delivering radiotherapy are based primarily on tumour size and nodal and metastases status, even though it is well known that tumours and their microenvironments are highly heterogeneous. In particular, it is well established that the local oxygen tension surrounding individual cells plays an important role in radiation-induced cell death, with hypoxic tumour regions responding poorly to irradiation. Therefore, to improve present radiation protocols, it is important to understand more fully the spatiotemporal dynamics of oxygen within a growing tumour before and during fractionated radiation. To this end, we have extended a spatially-resolved mathematical model of tumour growth first proposed by Greenspan (Stud. Appl. Math., 1972) to investigate the effects of oxygen heterogeneity on radiation-induced cell death. In more detail, cell death due to radiation at each location in the tumour, as determined by the well-known linear-quadratic model, is assumed also to depend on the local oxygen concentration. The oxygen concentration is governed by a reaction-diffusion equation that is coupled to an integro-differential equation that determines the size of the assumed spherically-symmetric tumour. We use a combination of numerical and analytical techniques to investigate the dynamic response of different heterogeneous tumours to radiotherapy. Model simulations reveal a rapid transient increase in hypoxia upon re-growth of the tumour spheroid post-irradiation, resulting in the fast re-emergence of a hypoxic cell population. We investigate the response to different fractionation schedules and identify a tumour-specific relationship between inter-fraction time and dose per fraction for a protocol to achieve cure. The rich dynamics exhibited by our model suggest that spatial heterogeneity may be important for predicting tumour response to radiotherapy for clinical applications.
SMB 2017 Contributed Talk Abstract

Title:

Modelling the spatiotemporal dynamics of chemovirotherapy cancer treatment

Authors:

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Area: Cancer

Chemovirotherapy is a combination therapy with chemotherapy and oncolytic viruses. It is gaining more interest and attracting more attention in the clinical setting due to its effective therapy and potential synergistic interactions against cancer. In this paper, we develop and analyse a mathematical model in the form of parabolic non-linear partial differential equations to investigate the spatiotemporal dynamics of tumour cells under chemovirotherapy treatment. The proposed model consists of uninfected and infected tumour cells, a free virus, and a chemotherapeutic drug. The analysis of the model is carried out for both the temporal and spatiotemporal cases. Travelling wave solutions to the spatiotemporal model are used to determine the minimum wave speed of tumour invasion. A sensitivity analysis is performed on the model parameters to establish the key parameters that promote cancer remission during chemovirotherapy treatment. Model analysis of the temporal model suggests that virus burst size and virus infection rate determine the success of the virotherapy treatment, whereas, travelling wave solutions to the spatiotemporal model show that tumour diffusivity and growth rate are critical during chemovirotherapy. Simulation results reveal that chemovirotherapy is more effective and a good alternative to either chemotherapy or virotherapy, which is in agreement with the recent experimental studies.
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B. Title And Abstract

Title: Mathematical Model of HPV and the Disruption of Tissue Homeostasis
Abstract: Human papillomaviruses (HPVs) are viruses that infect mucous membranes and skin. These tissues consist of epithelial cells that are organized into two major compartments. The first compartment consists of basal cells, which are attached to the underlying basement membrane. The basement membrane is rich in growth factors (GFs), which basal cells require for cell division. Due to their proximity to GFs, basal cells are typically the only epithelial cells that are able to divide. The second compartment consists of suprabasal cells, which are cells that have exited the cell cycle and differentiate as they migrate away from the basal layer. After several weeks these differentiated cells are shed from the upper layers of the epithelium. Epithelial tissue maintains homeostasis by ensuring that there is a balance between cell division and differentiation. Therefore, a basal cell must divide in order to replace a differentiated cell that is shed from the tissue surface.

HPVs infect basal cells. To enable the viral life cycle, HPVs disrupt normal control mechanisms of tissue homeostasis and enable cells to continue to express DNA replication enzymes, which leads to viral DNA synthesis and sometimes cell proliferation in the suprabasal layer. HPVs also have the potential to interfere with other regulatory mechanisms such as mode of cell division (symmetric vs. asymmetric), rate of cell division, and basal layer cell density. We construct a system of PDEs and a cellular automaton model to explore how modifications to key tissue regulatory mechanisms affect the duration and spread of infected cells throughout a tissue and potentially lead to benign or malignant tissue growth.
SMB Annual Meeting 2017

Authors: Inmaculada Sorribes (Presenter), Dr. Harsh Jain

Title: Cell Repair Mechanisms Responsible for Chemotherapy Resistance in Brain Tumors.

Abstract: Patients diagnosed with glioblastomas are expected to survive only 14 months due to chemotherapy resistance. The mechanisms of cell repair responsible for chemotherapy resistance are very complex and not well understood. Developed in collaboration with experimentalists we present a mathematical model of the repair pathways in a single cell. We then use it to create an age-structure population model that simulates the treatment of glioblastoma with standard chemotherapy (Temozolamide). By incorporating detailed mechanisms of drug actions, we predict the potential of DNA-repair enzymes inhibition in improving patient survival times.
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B. Title and Abstract
Evolution of treatment resistance in advanced prostate cancer

Recurrent and advanced prostate cancers are typically treated with total androgen blockade. However, androgen deprivation almost inevitably leads to castration resistance. Molecular mechanisms of castration resistance have been elucidated—the most common of which is amplification of the androgen receptor (AR) gene. But the ultimate cause of resistance remains unknown. Two hypotheses have been suggested: (i) resistance arises from cell plasticity; and (ii) resistance is caused by natural selection acting on mutant clones within the tumor. Here we show that evolution by natural selection is likely to be the ultimate cause of treatment resistance in prostate cancer. We found that, in a sample of 55 patients treated with intermittent androgen deprivation, the velocity of serum prostate specific antigen (PSA) decline tends to decrease over sequential on-treatment phases. In contrast, off-treatment PSA velocity exhibits no specific pattern in sequential cycles. These observations are consistent with treatment generating directional selection for castration resistance during treatment periods only. These results corroborate a predictive mathematical model that includes natural selection for AR expression under androgen deprivation. Such a model promises to be a key tool in managing castration protocols to mitigate the effects of treatment resistance in prostate cancer.
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B. Title and Abstract
EMERGENCE OF CHEMOTHERAPEUTIC RESISTANCE IN A EVOLUTIONARY GAME THEORETIC MODEL

Understanding the many ways in which cancers can develop resistance to targeted therapies is of grave importance. There is increasing evidence that the emergence of resistance is due not only to genetic alterations within the cancer cells themselves, but also due to the effects of the tumor microenvironment. Interactions between cancer cells and their supporting stromal cells can allow cancer cells to evade targeted therapies through often poorly understood means. We model the interactions between non-small cell lung cancer (NSCLC) cells--both sensitive and resistant to anaplastic lymphoma kinase (ALK) inhibition--and fibroblasts through a three-strategy evolutionary game theoretic approach. Building on earlier work in this field, we create a payoff matrix, derive analytic solutions to equilibria, and compute numerical simulations for both pre- and post-treatment states. We show that therapies can have large qualitative and quantitative effects on the dynamics of the evolutionary game. This work furthers the theoretic background for the development and tailoring of therapies for ALK+ NSCLC by investigating the role of fibroblasts as drugs that target fibroblasts already exist. It can also further understanding of the potential differences that changing the timing of therapies can have on the evolution of resistance to targeted chemotherapeutics.
Group 3: Cell Biology

Buttenschoen A.
April 4, 2017

Planning

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The presenter’s name is in **bold** font.

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2 B. Title and Abstract

**Title:** A space-jump derivation for non-local models of cell-cell adhesion.

**Abstract:** Cellular adhesions are one of the fundamental biological interactions between cells and their surroundings. However, the continuum modelling of cellular adhesions has remained mathematically challenging. In 2006 Armstrong et. al. proposed a mathematical model in the form of an integro-partial differential equation. This model was successful at replicating Steinberg’s cell sorting experiments, and since has been used in models of cancer invasion and morphogenesis.

In this talk, we present a derivation of the cell-cell adhesion model from an underlying stochastic random walk. The key concept of this derivation is the cell’s polarization vector. Several key micro biological properties are included in the polarization vector. I will show that a particular choice of these properties yields the original cell-cell adhesion model as proposed by Armstrong et.al. I will conclude this talk by discussing numerical solutions that exhibit pattern formation.

This is joint work with T. Hillen, K.J. Painter, A. Gerisch.
Effect of radiation on the cell cycle through mathematical modelling

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Abstract

The cell cycle comprises a chain of events that results in the division of a cell into two daughter cells. It is carefully regulated by a complex network of control mechanisms including cyclin-Cdk interaction, DNA replication and checkpoints. In particular, the G2/M checkpoint checks the integrity of the DNA before proceeding to mitosis. In the presence of DNA damage, the cell cycle is arrested in this checkpoint until the damage is repaired. Failure to activate or maintain this checkpoint causes genome instability and, in some cases, cancer cells. This is critically important in radiation therapy since it has been shown that G2/M checkpoint activation is compromised for low doses of radiation [3, 2].

Here, we study the effect of radiation on the cell cycle through a mathematical model based on a Minimal Cdk Network [1]. In our modified version of the model, we include a DNA damage pathway and study its effect on the cell cycle (represented by a stable limit cycle). We identify the G2/M checkpoint activation in the cell cycle with a saddle-node on an invariant circle (SNIC) bifurcation. For a small dose of radiation below a threshold, we observe that the period of the limit cycle increases (which corresponds to a delay in the progression into M-phase); for higher dose of radiation above the threshold, we observe a loss of the limit cycle and the appearance of a node and a saddle (corresponding to the activation of the checkpoint). We also observe that the G2/M checkpoint, determined by the saddle point, is located right before mitosis and depends dynamically on the amount of radiation. Our results provide a foundation for understanding many phenomena observed in low-dose radiation, including hyper-radiosensitivity and increased radioresistance (HRS/IRR) phenomenon observed in the study of survival fraction after radiation.

References


Cytosolic Liquid-Liquid Phase Transitions in Multinucleate Cells

Intracellular phase transitions are an emerging mechanism for cell organization. These membrane-less compartments are formed due to the occurrence of liquid-liquid demixing and subsequent concentration of cellular components in a specific region. By undergoing these localized phase separations, cells are able to create dynamic compartments that help maintain the regulation of biomolecular interactions, localize factors such as RNAs and proteins, and promote specific biochemistry. The utility of liquid-liquid phase transitions and the assembly of cytosolic compartments is especially critical in large, multinucleate cells. These types of cells are common in the biosphere and include skeletal muscle tissue, the placenta, many filamentous fungi, and certain types of cancer. An excellent model organism for studying liquid-liquid phase transitions in multinucleate cells is the branching fungus *Ashbya gossypii*. In *Ashbya*, Whi3, an RNA binding protein, works with two different RNA binding partners to form liquid droplets within the cell. Under normal physiological conditions, Whi3 alone cannot form liquid droplets, *in vitro*, as this is a phenomenon that only occurs once it is able to bind with RNA. When Whi3 binds with *CLN3* transcripts *in vivo*, the droplets formed by these complexes cluster around each individual nucleus, allowing them to maintain an asynchronous division pattern. Similarly, at the growth tips, once Whi3 binds the RNA *BNI1*, the liquid droplets that are formed are able to help establish cellular polarity. We use phase field modeling, with phase variables to represent the volume fractions of Whi3, RNA transcripts, and the complex they form, and we propose a modified Flory-Huggins free energy coupled with the complex fluid dynamics present in the cytosol. We report modeling and experimental progress on these cytosolic liquid-liquid phase transitions in *Ashbya* as they help guide our understanding of the mechanisms behind droplet formation in the cytosol, as well as how these droplets function in cellular regulation.
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B. Title:
Modelling persistence in motion in cell migration at multiple scales

Abstract:
Neural crest cells, are cells of the early embryo that contribute to diverse tissue types in adult vertebrates. Failure of neural crest cells to travel to their target locations can result in a wide range of birth defects collectively known as neurocristopathies. Melanocytes are a sub-population of neural crest cells responsible for the pigmentation. The migration of melanocytes has been modelled in some detail with traditional agent-based models on lattice space aside complementary probability master equations and partial differential equations describing the average behaviour of these agents. However, these models fail to include some biological features that may play an important role in the macroscopic dynamics. For example, the machinery which allows cells to migrate in a particular direction takes time to assemble and disassemble, meaning that cells persist in their direction of motion. Cellular persistence of motion has thus far been ignored in existing models of melanocyte migration, but may play an important role in the efficient colonisation of the developing epidermis. In this project we investigate new methods of incorporating persistence into these descriptive mathematical models and how this phenomenon affects the collective behaviour of cells in a large scale.
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B  Title and Abstract

Length distribution dynamics of intermediate filaments

We model the temporal evolution of length distribution of intermediate filaments. Using the framework of the Gaussian semiflexible chain model, and the biopolymers physical properties, we compute the association rate constants between filaments of different lengths. The simulated length distributions then are compared to experimental distributions for intermediate filaments vimentin and keratin obtained in vitro.
Numerical investigation of skin burn injuries with cell regeneration using wavelet method

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The accurate analysis of the skin burn process is of critical concern not only for fundamental understanding of the thermoregulation but also for the development new animal models. In this article, we have developed a one-dimensional multi-layer dual-phase-lag model to characterize the skin burn injuries while considering the cell regeneration processes. The transient temperature distribution on skin surface was numerically calculated using a new wavelet based hybrid numerical scheme. A damage function denoting the extent of burn injury was then calculated using the modified Arrhenius assumptions. The effect of thermal properties, lag times and different geometrical dimensions on temperature profile and damage function have been investigated. The burn injury distribution with and without regeneration of cell has been compared graphically. The authors have belief that present study will be more useful for medical doctors in the clinical field for better understanding of burn injury.
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B. Title and Abstract
- Title: Modeling the effects of Aβ on calcium signals through IP\(_3\) receptors.

  Abstract: Alzheimer’s disease (AD) is a devastating illness affecting millions of people globally. Although the cause of this disease remains unknown, recent studies have focused on Amyloid beta (Aβ) peptides as a possible factor in the pathogenesis of AD. The slow accumulation of Aβ has been shown to alter calcium signaling mechanisms causing cytotoxic effects that can lead to a gradual decline in memory, cognitive skills, and eventually neuronal death. In this study we use mathematical modeling and analysis to study the effects of Aβ on calcium regulation by specifically tracking the contribution through the 1,4,5- Inositol-triphosphate (IP\(_3\)) receptor. Our goal is to better understand how various levels of Aβ affect the IP\(_3\) production cascade and leads to subsequent calcium release through IP\(_3\) receptors on the endoplasmic reticulum. To do this, we formulate a model for tracking the IP\(_3\) concentration and incorporate this model into a closed-cell calcium model. We investigate the behavior of the calcium model under various parameter regimes and explore how different levels of Aβ affect model solutions. We use experimentally observed data to compare our results and look to precisely identify the physiological processes in the IP\(_3\) production mechanism that are directly influenced by Aβ. These results can then be used to better understand the role that Aβ plays in altering normal neuronal calcium signals.
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SMB 2017 Poster Abstract

Part A

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Part B

Title: Understanding zebrafish pigmentation patterns through mathematical modelling

Abstract:
Zebrafish pigment pattern formation is the mechanism by which three pigment cell types (xanthophores, melanophores and iridophores) interact to produce the blue and yellow striping pattern seen in adult zebrafish. Without any one of these pigment cell types, the conventional striping pattern does not occur.

Considerable theoretical and experimental investigations have prompted hypotheses that a Turing-type reaction-diffusion mechanism may be responsible for the striped pigment pattern of zebrafish. This type of model suggests that morphogens or “form generator” molecules pre-determine the pigment pattern by reacting with each other and diffusing across a domain.

However, recent experimental studies suggest that the mechanism uses cell-cell interactions, rather than the classic pre-pattern-generating pair of interacting, diffusible ligands. On-lattice volume-exclusion models are an example of a mathematical representation that can explicitly incorporate these cell-cell interactions. In these models cells are represented as agents on a lattice. Agents can move to nearest-neighbour lattice sites provided the space it tries to move into is unoccupied. These models can be simulated stochastically and their continuum analogues analysed deterministically. The advantages of these models over other Turing-type models are that unlike their counterparts, they can incorporate the fluctuations inherent in biological systems; finite cell size effects are not neglected and the crucial role of iridophores and ASIP signalling can be included.

As part of this interdisciplinary project, a detailed investigation of this type of model to produce pattern formation, including the relationship between key length scales in the model, the system size and compartment size, and their impact on the patterns formed, will be carried out. Subsequently, hypotheses on pigment cell interactions will be explicitly encoded in this framework to explore the potential of the model to replicate the patterns on both wild-type and mutant fish.
Modeling Actin Regulations by Cofilin in Motility Structures of Cancer Cells

Cofilin is an important regulator of actin polymerization and cell motility. It severs old actin filaments, generates new barbed ends, and thus allows actin polymerization to continue from previously capped filaments. We have built mathematical models and analyzed the dynamics of cofilin activation and subsequent actin growth dynamics on two distinct motility structures seen in metastatic mammary carcinoma cells, namely lamellipodia and invadopodia. At first glance, it appears that cofilin plays similar roles during the early dynamics/formation of these two distinct motility structures. EGF stimulation induces cofilin activation followed by a peak of actin barbed ends on the timescale of 1 min. We had previously characterized the regulation of cofilin within the lamellipodia using mathematical modeling. There, cofilin severs capped actin-filaments spurring further growth. We then asked whether similar assumptions on kinetics and regulations seen in the lamellipodia can explain the actin dynamics data obtained from the invadopodia. We found that a simple extension of our previous model failed to capture the observed data. These differences led us to look further into differences between lamellipodia and invadopodia. We used mathematical modeling to further quantify the effects geometry, the availability of actin monomers, and the role of other actin regulators, in shaping the actin dynamics during the initial stage of invadopodia formation.
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2 Presenter

B. Title and Abstract

A mathematical model of DNA methylation dynamics in somatic cells

DNA methylation is an important epigenetic mechanism used by cells to control gene expression. Interestingly, DNA replication, a function necessary for cell division, disrupts the methylation pattern. Since perturbed methylation patterns are associated with aberrant gene expression and disease, DNA methyltransferases (DNMTs) must restore the correct pattern following DNA replication. However, the exact mechanisms of this restoration remain under investigation. We propose a mean-field model to study the dynamics of post-replicative restoration of methylation patterns.

DNMTs perform methylation by adding a methyl group to cytosines at CpG sites, in which cytosine and guanine are consecutive in the DNA. These CpG sites are found in regions of high density, termed CpG islands (CGIs), and regions of low density in the genome. Nearly every CpG site in a CGI has the same state, either methylated or unmethylated. Meanwhile, nearly all CpG sites in regions of low density are methylated. We developed a stochastic model for the restoration of the methylation pattern following replication by considering the methylation activity of DNMTs, the activity demethylating enzymes, and possible interactions with replication fork proteins. Our model predicts that the methylation of CGIs exhibits bistable behavior. Furthermore, we predict that methylated CGIs are primarily maintained by the processivity of DNMTs, while the methylation of CpG sites outside of CGIs is driven by localization of DNMTs to the replication fork.
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B Poster Title: Chemotactic Cell Migration Models for the Zebrafish Posterior Lateral Line Primordium

Abstract: The zebrafish posterior lateral line, a sensory network that detects water movement patterns, is an excellent system for studying the mechanisms that drive collective cell migration. Migration of the zebrafish posterior lateral line primordium (pLLP) is driven by polarity in the expression of CXCR4b and CXCR7b, which are receptors for the chemokine ligand CXCL12a. This receptor polarity leads to a local gradient in CXCL12a expression, with higher levels of CXCL12a in the direction of migration. Using migration of the pLLP as motivation, we use mathematical models to compare a variety of chemotactic cell migration situations: individual vs. collective cell migration, pre-imposed vs. self-generated signaling gradients, and uniform receptor expression vs. receptor polarization. We show that efficient directed migration of the pLLP is only possible when primordial cells are cohesive and CXCR7b activity is restricted to the trailing end of the primordium.
**MET Transition in Somite Formation using Cellular Potts Model**

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Somites are segments formed during somitogenesis which in later developmental stages become parts of multiple tissues. Somite formation has been extensively studied from the perspective of the clock and wavefront and local reaction diffusion mechanisms[1,2]. In this work however we model mesenchymal to epithelial transition in somite formation as the self organizing mechanism that drives morphogenesis. It is known that during the process mesenchymal cells attain structure and polarity through the formation of basal and apical protein expressing domains[3]. This internal polarity and organization can be initiated through interaction with extra cellular matrix components like Fibronectin[4]. We model this transition from undifferentiated mesenchyme to elongated epithelial using the Cellular Potts Model[5] and achieve external organization and cell to cell communication by the establishment of a long range order through chemical diffusible signals. This work suggests an alternative mechanism for somite formation.

References:


5. Francois Graner and James A.Glazier Simulation of Biological Cell Sorting Using a Two-Dimensional Extended Potts Model (1992)
Influenza epidemics result in a public health and economic burden around the globe. Traditional surveillance techniques, which rely on doctor visits, provide data with a delay of 1–2 weeks. A means of obtaining real-time data and forecasting future outbreaks is desirable to provide more timely responses to influenza epidemics. We used Internet traffic data from the Centers for Disease Control and Prevention website to determine the potential usability of this data source. We tested the traffic generated by ten influenza-related pages in eight states and nine census divisions within the United States and compared it against clinical surveillance data. Our results show an $r^2$ of 0.955 in the most successful case and promising results for other cases. These results demonstrate that internet data can complement traditional influenza surveillance, especially when there is a time lag or data is unavailable. We anticipate the traffic generated from the CDC website may be useful for disease surveillance and informing nowcasting and forecasting models.
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B. Title and abstract
Application of the Immersed Boundary Method to Epithelial Bending

Computational modelling can provide a useful framework within which to investigate multicellular structures on an individual cell based level. Feedback between experimental data and computational modelling can help inform experimental design and elucidate underlying biological processes. Here, we present a computational investigation of mechanics involved during early stages of embryonic tooth-bud formation in the mouse embryo. Working closely with experimental collaborators, we have applied computational modelling to help understand the role of cell-cell interactions in larger tissue-level processes such as 'vertical telescoping' during the epithelial bending observed in the tooth bud system. In doing so, we have developed an Immersed Boundary framework to model the cross section of an epithelial sheet, which incorporates a fine-grained resolution of cell shapes while allowing individual cell-cell interactions to be probed. The framework can incorporate biological data such as cell shape, incidence of proliferation, and localised transmembrane protein concentrations. By numerically simulating hypotheses about the mechanical structure of individual cells, we address the following question: to what extent can simple mechanical inhomogeneities in the cortical stiffness of individual cells explain the observed epithelial bending during the early stages of tooth bud morphogenesis.
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B. Title and Abstract

Feedback Analysis in the Kidney

The mammalian kidney maintains the balance of water, salt and blood pressure of the body. A published model simulates hemodynamic control in the kidney by representing the interactions between autoregulatory mechanisms, including the myogenic response, the tubuloglomerular feedback and the connecting tubule glomerular feedback. In this study we aim to extend that model to include more realistic tubular water transport, and to apply that model to investigate the impact of positive and negative feedback on renal blood flow oscillations.
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Title: Bayesian Estimate of the Parameters of a Stochastic Differential Model of HIV Incidence in the United States

Abstract:

Current estimates of the HIV epidemic indicate a decrease in the incidence of the disease in the undiagnosed subpopulation over the past 10 years. However, a lack of access to care has not been considered when modeling the population. Populations at high risk for contracting HIV are twice as likely to lack access to reliable medical care. In this project, we consider three contributors to the HIV population dynamics: susceptible pool exhaustion, lack of access to care, and increased prevalence of preventative medication. We consider the change in the proportion of undiagnosed individuals as the parameter in a simple first-order autoregressive model. We obtain a conservative estimate using hierarchical Bayesian statistics. A system of stochastic differential equations is used to obtain probability estimates for the trend in the population. The proportional change is used to derive epidemic parameter estimates in an extended model. Finally, we present likelihoods and analytic solutions for the three hypothesized contributors to the trend in the undiagnosed HIV incidence.
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B. Title and Abstract

TITLE:
Synchronization hubs may arise from rhythmic inhibition in gamma oscillations

ABSTRACT:

Neurons in the visual cortex exhibit heterogeneity in feature selectivity and the tendency to generate action potentials synchronously with other nearby neurons. By examining visual responses from cat area 17 recorded using multielectrode arrays, we find that, during gamma oscillations, there is a positive correlation between each unit’s sharpness of orientation tuning, strength of oscillations, and propensity towards synchronization with other units. Units that exhibit a particularly high synchronization propensity we term synchronization hubs; such units typically exhibit strong oscillations in their firing output and sharp orientation tuning curves. Using spiking neuron models, we demonstrate that heterogeneity in the strength of rhythmic inhibitory inputs can account for the correlations between these three properties in a parsimonious way. Neurons subject to strong inhibition tend to oscillate strongly in response to both optimal and suboptimal stimuli and synchronize promiscuously with other neurons, even if they have different orientation preferences. Moreover, these strongly inhibited neurons can exhibit sharp orientation selectivity provided that the inhibition they receive is broadly tuned relative to their excitatory inputs. These results predict that the strength and orientation tuning of synaptic inhibition are heterogeneous across area 17 neurons, which could have important implications for these neurons’ sensory processing capabilities. Furthermore, although our experimental recordings were conducted in the visual cortex, our model and simulation results are capable of being applied more generally to any brain region with analogous neuron types in which heterogeneity in the strength of rhythmic inhibition can arise during gamma oscillations or their analog.
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Title and Abstract
Using Mixed Effects Modeling to Analyze Patients with Diabetic Foot Ulcers

Because the medical treatment of diabetic foot ulcers remains a challenge for clinicians, a quantitative approach using de-identified patient data and mathematical modeling can help researchers understand the physiology of the wounds. In this work, we plan to use nonlinear mixed effects modeling to attribute wound healing variability to either fixed effects, parameters that are more likely to remain constant for all patients, or random effects, parameters that vary from patient to patient. We aim to identify these random effects to make sure these parameters are taken into special consideration when treating patients with chronic wounds, especially diabetic foot ulcers. We will also use Latin Hypercube Sampling (LHS), a stratified sampling method, in conjunction with partial rank correlation coefficient (PRCC), computed from a multivariable regression analysis, to identify the sensitivities of parameters. The goal of this project is to utilize individual patient data to identify key parameters, through the use of nonlinear mixed effects modeling, LHS, and PRCC, in the healing process in order to improve patient care and diagnosis.
SMB 2017 Poster Abstract

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Title:
A continuum model of growth with active patterning

Abstract:
We implemented a computational model of generalized tissue growth based on the Stokes equation for growth dynamics, coupled with a classical reaction diffusion system for patterning. Our work draws inspiration from existing literature, but to our knowledge this is the first time that active patterning has been coupled with Stokes flow in full 3D simulation. Furthermore, unlike the previous works which control the free boundary through mesh deformations, we treat the free boundary as an implicit surface, allowing us to perform all computations in a static mesh. While our initial motivation for constructing the model is simulating tooth morphogenesis, our focus in this poster is on some of the basic principles of the model, rather than simulating the growth in any specific biological system.
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B. Title: Modeling nucleosomal DNA in living yeast: Nucleolus dynamics and structure

Abstract: The genome in living yeast cells is a highly dynamic system where entropic interactions and nuclear confinement drive the formation of domains of high chromosomal interaction, known as topologically associating domains. We investigate dynamic
Identifying Optimal Sampling Distributions for Individual Patients

In this work, we utilized a previously developed mathematical model describing the interactions among matrix metalloproteinases, their inhibitors, extracellular matrix, and fibroblasts (Krishna et al., 2015). The model was modified and curve-fitted to individual patient data from Muller et al. (2008), while model parameters were estimated using ordinary least-squares. Model parameters can be estimated more efficiently and accurately by implementing an optimal design method that calculates optimal observation times for collecting clinical data. We introduce a SE-optimal design (standard-error optimal-design) by using a Fisher Information Matrix (FIM) to determine the optimal final times for each patient. The goal of this work is to quantify and understand differences between patients to predict future responses and individualize treatment for each patient.
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Organoid3D: the role of microenvironmental heterogeneity on the development of breast tumor spheroids elucidated with computational modeling

The irregular topology of tumor vasculature and heterogeneous tumor tissue architecture lead to the development of gradients in chemical and physical cues within the surrounding extracellular matrix. The resulting disruption in oxygen transport, accumulation of acidic products, and elevated mechanical tension commonly observed in the tumor tissue, mutually affect tumor progression and its response to therapies. Furthermore, the microenvironmental conditions dynamically evolving after treatment alleviate efficacy of anticancer drugs and are difficult to investigate in vivo.

To represent the complexity and dynamics of tumor microenvironmental heterogeneity we developed Organoid3D—a computational model of human breast cell cultures integrated with organ-on-the-chip experiments. The computational model was validated based on the data collected from cultured breast cell spheroids, including the non-tumorigenic epithelial cell line MCF-10A, mildly tumorigenic c-Ha-ras oncogene transfected cell line MCF-10AT1, and a metastatic cell lines MCF-10CA-1a and MCF-10CA-1d. Exploiting the differences in these cell lines genetic profiles, cell mechanical properties, and image guided variations in morphologies, Organoid3D reproduced the dynamics of growth of 3D acini and tumor spheroids under various microenvironmental conditions. Subsequently, we applied the calibrated model to predict tumor response to chemotherapy in heterogeneous microenvironments consisting of dynamically changing gradients of oxygen and pH, as well as tension of the surrounding microenvironment. The overarching aim of our project is to use this integrated (in silico-organ and organ-on-the-chip) approach to target the treatment of tumor 3D organotypic cultures with drugs that display different mechanism of action, such as cell cycle arrest, initiation of apoptosis, or treatment combinations.
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B. Title and Abstract
Title: Decomposing leaf hydraulic conductance with a hybrid numerical method
Abstract: We present analysis of a hybrid numerical method used to solve an initial value problem where an unknown parameter is chosen to satisfy one additional boundary condition. Physically, the determination of the unknown parameter is equivalent to decomposition of total leaf hydraulic conductance into components in the axial and radial directions.
File: Pierro_Jocylin
Subject: SMB 2017 Poster Abstract

Content
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B. Title and Abstract
Title:
Modeling the Effect of Perfluorooctanic Acid on the Survival of Loggerhead Sea Turtle Cells

Abstract
Toxicokinetic and toxicodynamic (TKTD) models are increasingly applied to environmental risk assessments to predict the effects of pollutants in living organisms. In our study the TKTD model General Unified Threshold model of Survival (GUTS) was parameterized using targeted in vitro data, and applied to predict the lethal effects of Perfluorooctanic Acid (PFOA) on endangered loggerhead sea turtle (Caretta caretta) cells over time. PFOA is known to cause changes in inflammatory and immune responses as well as cytokine production in reptiles and has been detected in loggerhead tissues. TKTD modeling has two modeling approaches for survival: stochastic death (SD) and individual tolerance (IT). In SD models one toxic concentration threshold is identical for all individuals. When the internal concentration in the organism exceeds this threshold, the predicted survival decreases equally among individuals. IT models are taking into account inter-individual sensibility to toxicants, where the response to the stressor varies among individuals. GUTS models are novel in including both SD and IT model approaches. In this study, we analyzed for the first time the survival of loggerhead cell populations, using both modeling approaches. Effectiveness of the two models will be analyzed using profile likelihoods, confidence intervals, and r-squared. This study will create a paradigm for toxicological studies in sea turtles by extrapolating the toxic effects from cells to individual sea turtles, using survival likelihood endpoint, and assessing the use of a less-invasive tool to monitor toxicological effects of marine contaminants in an endangered marine species.
A. Authors: Thalia Rodriguez (Presenter) and Dr. Hana Dobrovolny

B. Title And Abstract:

Quantifying the Impact of Trypsin on In Vitro Viral Infections

Many viral experiments are done in vitro, however, not all cell lines used in these experiments possess the proteases necessary to enhance infectivity. Trypsin is a protease used to facilitate different viral in vitro infections, for example influenza and rotaviruses. Trypsin cleaves the viral surface protein hemagglutinin, allowing it to fuse with the cell membrane and enter the cell. We use data from different in vitro infections in the presence and absence of trypsin to parameterize a within-host mathematical model of viral infection. This allows us to quantify the dynamical changes caused by the presence of trypsin.
MeshmerizeMe: A Tool for the Creation of Curvilinear Meshes for Immersed Boundary Simulations

Authors: Michael Senter, Laura Miller

When running immersed boundary simulations with IB2d or IBAMR, one challenging step consists of defining the geometry for the simulation. Usually this is done by hand coding scripts that traverse user-defined curves to find points that can recreate the desired geometry. For many geometries of interest, images are available from which the user tries to extract functions that could be used to represent parts of the geometry. MeshmerizeMe is being developed to aid in the process of creating the curvilinear mesh used in immersed boundary methods. The software takes a vector graphics file along with some basic information regarding the desired simulation and returns the points on the curvilinear mesh needed by immersed boundary code like IB2d. This automated method of creating geometries has the potential of reducing the amount of time needed to translate between an image the researcher has in mind and the files the simulation software needs.
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B. Title and Abstract

**Title:** Optimal control of vaccination rate in an epidemiological model of *Clostridium difficile* transmission

**Abstract:**  
The spore-forming, gram-negative bacteria *Clostridium difficile* can cause severe intestinal illness. A striking increase in the number of cases of *C. difficile* infection (CDI) among hospitals has highlighted the need to better understand how to prevent the spread of CDI. In our paper, we modify and update a compartmental model of nosocomial *C. difficile* transmission to include vaccination. We then apply optimal control theory to determine the time-varying optimal vaccination rate that minimizes a combination of disease prevalence and spread in the hospital population as well as cost, in terms of time and money, associated with vaccination. Various hospital scenarios are considered, such as times of increased antibiotic prescription rate and times of outbreak, to see how such scenarios modify the optimal vaccination rate. By comparing the values of the objective functional with constant vaccination rates to those with time-varying optimal vaccination rates, we illustrate the benefits of time-varying controls.
SMB 2017 Poster Abstract

A) Authors:

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B) Title and abstract

Title:

Defective Interfering Particles: Intracellular interference in Poliovirus

Abstract:

Defective Interfering Particles (DIPs) are virus-derived particles which lack key genetic regions for completion of their viral cycle. Design of new antiviral strategies through DIPs is a promising field of research. For a long time, it has been known that DIPs are produced in nature and interfere with wild type strain but usually are displaced. The underlying mechanisms of interference are yet to be unravelled. Poliovirus is a model virus for encapsidated single strand RNA⁺ viruses such as Dengue or Zika. The engineered DIP lacks a genomic region encoding viral capsids and thus DIP infection can result in production of new DIPs only when they coinfect a host cell with the wild-type strain.

To fully understand key parameters intervening in DIP interference, we use a combination of mathematical modelling, numerical simulations and experiments.

We present a deterministic intracellular model of DIP interference. Using data-driven design and calibration, we investigate specific factors inhibiting poliovirus replication and virion production in cells coinfected with DIP and wild-type poliovirus. Our model shows that competition for specified cell resources and capsid stealing are key processes in intracellular interference. Model predictions are used to assist experimental set-up and as an input for our subsequent model of intercellular spread. For more details on intercellular model, see Dr Elsa Rousseau’s presentation.
Group 5: Dynamical Systems

PS47
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B: Title and Abstract

Mechanical constructs of population survival dynamics

A niche biogerontological research area of general population dynamics, derived from reliability theory, is that of survival and longevity analysis. In such studies there is a closed system consisting of an initial cohort of similar individuals whose aggregate macro-state, characterized by the survival fraction of the initial population, evolves through the irreversible transition of individual members from the state “alive” to the state “dead”. The status of each individual is limited to these two Boolean states regardless of size or physiological condition and the status cannot be exchanged with an individual of opposite state.

In previous work we have determined that a measure of gerontological distance in such systems can be specified as the negative of the natural logarithm of the survival fraction of the initial population, thus providing a basis for the concepts of a velocity of aging and an acceleration of aging in analogy with dynamic variables from classical Newtonian mechanics and physics. We now extend this by formulating other analogous macroscopic deterministic mechanical constructs of momentum, force, kinetic energy, potential energy, and power. Statistical-based constructs of entropy and “temperature” of population aging are also developed by considering every permutation of alive/dead status for each of \( N \) initial population members as \( N^2 \) unique micro-states, only one of which can be occupied at any particular moment of time.

The results obtained are applicable to any system whose initial cohort size is large enough and whose time resolution small enough that the initial population survival fraction can be approximated as a continuous and continuously differentiable function of time or age. Several parametric models (\textit{e.g.}, Gompertz, Gompertz-Makeham, Weibull) satisfy this condition, but we focus on the Gompertz Model for illustrative purposes. This is a model with two parameters, \( h_0 \) and \( \gamma \), which can be defined by the time derivative of the survival fraction as \( \dot{S} = h_0 e^{\gamma t} \).

As an example of use of these mechanical constructs in a biological context we fit a Gompertz Model with parameters derived from maximum likelihood estimates of rat population survival data reported in the classic dietary restriction study of Yu \textit{et al.} (J. Gerontol. 40, 657-670, 1985). The survival fraction and the potential energy time dispersion profiles have the familiar reverse sigmoidal shape, while the velocity of aging and constructs derived from it such as momentum, force, and kinetic energy have a unimodal peak profile.
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B. Title And Abstract

“Particle Diffusion and Competitive Receptor Binding”

We consider a setup in which $n$ particles are initially released into an environment and diffuse freely. Much of the domain boundary is absorbing, where the particles can exit the domain. The rest of the boundary consists of patches that we call “receptors” and that can switch between being reflecting and absorbing. An absorbing receptor turns reflecting (“unavailable”) once a particle collides with it; a reflecting receptor turns absorbing (“recharges”) spontaneously after spending a random amount of time in the reflecting state. We are interested in the distribution of the number of particles that are captured by the receptors. We find that the number of the receptor-captured particles has an upper bound of the order of $(\log n)$. We explore parameter ranges where this upper bound is tight, compare behavior in multiple dimensions, and discuss the implications of this $\log n$ behavior in the context of neurotransmitter release.
SMB 2017 Poster Abstract

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*Presenting author

B. Title And Abstract

Title: Modeling Daphnia growth under concurrent stoichiometric and toxicological constraints

Abstract: Accurately assessing the risks of contaminants requires more than an understanding of the effects of contaminants on individual organisms, but requires further understanding of complex ecological interactions, elemental cycling, and the interactive effects of natural stressors, such as resource limitations, and contaminant stressors. There is increasing evidence that organisms experience interactive effects of contaminant stressors and food conditions, such as resource stoichiometry and nutrient availability. We are developing and analyzing a series of empirically testable and robust mathematical models of populations dynamics subject to stoichiometric and contaminant stressors. In parallel to developing the models, we will integrate sufficient data from existing and new experiments to parameterize, test, and improve them. The synthesis of the models and experiments will result in the development of a robust theoretical framework appropriate for improved risk assessment applications in ecotoxicology that incorporate the effects of stoichiometric constraints on concurrent ecological and toxicological processes. In particularly in this poster we are presenting how Daphnia growth depends on the body phosphorus to carbon ratio, while this ratio depends on the Daphnia toxicant body burden.
A Study of Pharmacokinetic Model

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March 30, 2017

Abstract

The compartmental approach is an empirical procedure for pharmacokinetic modeling. This model has been used to derive many useful quantities by comparing the predicted values with actual data. However, in clinical operations, the resident time of a drug in the stomach may vary depending on the time for gastric emptying. The latter is affected by food uptake, other drugs, placebos, and other factors. Moreover, real pharmacological processes are always exposed to influences that are not completely understood or for which it is not feasible to model explicitly. Ignoring these phenomena the modeling may affect the estimation of PK/PD parameters and the derived conclusions. Therefore, there is an increasing need to extend the deterministic models to ones including a stochastic component. In order to get a more reliable analysis, in our study, we added a control vector to the Pharmacokinetic model, then used optimal control theory to analyze the modified model and find an equilibrium point; then, near the stationary point, we added white noise to the modified model and analyzed the stochastic differential equation. We prove existence and uniqueness of the system and get an explicit solution of the SDE.
HOW SHOULD BEHAVIOR BE TREATED IN COUPLED CONTAGION MODELS?

ABSTRACT. Properly incorporating behaviour is one of the largest challenges facing epidemiological modelers today. Behaviour has long been considered a ‘thought contagion’ in the social sciences and was modeled with SIS dynamics as early as 1964. Thus we have two contagious process that affect one another, disease and behavior. As such we have seen the development of so called coupled contagion models in the late 2000s. For the most part behaviour has been treated like a simple contagion spreading with mass action dynamics in these models. However, recent literature questions this assumption, positing that behaviour should rather be thought of as a complex contagion, requiring reinforcement from multiple sources before adoption occurs. In the past few years we have seen experimental evidence that suggests this is in fact the case. Understanding how to explicitly model behaviour is one of the main challenges of incorporating behaviour into models of infectious disease [1]. We examine this question with an ODE model of a coupled contagion process. In particular we demonstrate the qualitative dynamic differences between a simple contagion and complex contagion approach to modeling the spread of a preventative behavior.

REFERENCES

SMB 2017 Contributed Talk Abstract

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B. Title And Abstract

Title: Ecotoxicological Models under Stoichiometric Constraints

Abstract: Accurately assessing the risks of contaminants requires more than an understanding of the effects of contaminants on individual organisms, but requires further understanding of complex ecological interactions, elemental cycling, and the interactive effects of natural stressors, such as resource limitations, and contaminant stressors. There is increasing evidence that organisms experience interactive effects of contaminant stressors and food conditions, such as resource stoichiometry and nutrient availability. We are developing and analyzing a series of empirically testable and robust mathematical models of populations dynamics subject to stoichiometric and contaminant stressors. In parallel to developing the models, we will integrate sufficient data from existing and new experiments to parameterize, test, and improve them. The synthesis of the models and experiments will result in the development of a robust theoretical framework appropriate for improved risk assessment applications in ecotoxicology that incorporate the effects of stoichiometric constraints on concurrent ecological and toxicological processes.
Presenter: Bruce Pell

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Title: Data-Based Modeling and Implications of Within-Host Dynamics of Barley Yellow Dwarf Virus

Abstract:
Understanding how diseases influence growth and nutritional value of plants is a significant challenge for supporting a growing human population and satisfying its demand for sustainable food and fuel resources. From a disease ecology perspective, recent studies have shown that the dynamics of within-host pathogen populations are intimately linked to their resource supply and host elemental composition. Here we model the intertwined dynamics of plant carbon mass, within-host nutrient resource levels and virus dynamics using a system of differential equations to aid in understanding experimental data from the complex relationships between Avena Sativa and Cereal/Barely Yellow Dwarf Virus.
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2 Title And Abstract

Title: Infectious viral dynamics of cellular coinfection in human respiratory tract

Abstract: Respiratory viral infections are a leading cause of mortality worldwide. As many as 40% of patients hospitalized with influenza-like illness are reported to be infected with more than one type of viruses. Mathematical models can be used to help us understand the dynamics of respiratory viral coinfections and their impact on the severity of the illness. We develop a mathematical model which allows for respiratory cells to be infected simultaneously with two types of viruses. A mathematical analysis is performed to assess the full behavioral dynamics of the model. We find that chronic coinfection does not occur in this model; infection grows due to only one viral species. Some other mechanism must be responsible for the long-lasting coinfections in humans.
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B. Title and Abstract

Stochastic simulations of HIV persistence

Human immunodeficiency virus (HIV) remains a difficult global challenge. While the virus can be controlled with daily antiretroviral therapy (ART), not all infected patients can access medication, and a cure is needed to decrease the global burden of disease. Ongoing controversy surrounds mechanism by which HIV virus returns to pre-treatment levels when therapy stops. Evolutionary dynamics provide a key to understanding this question. When the virus infects new cells, errors are common and mutations accrue sequentially, driving genetic divergence from the initial infecting virus. Signatures of evolution dictate that ongoing replication at low levels might be the cause of persistence on ART. However, much evidence points to proliferation of latently infected cells as the persistence mechanism. While latent, cells remain infected but do not produce virus thus avoiding immune clearance. In this scenario, evolution should not be observed. We simulate viral dynamics with a stochastic branching process model, and develop analytical extinction probabilities. The model fits to multi-phasic decay of the HIV viral load upon initiation of ART, recapitulates observed viral evolution patterns and predicts rough equivalence between latent and sanctuary populations soon after initiation of ART. We find, in agreement with existing data, that latent proliferation is the predominant mechanism on long term ART. Additionally, our hypothesis of decreasing T cell activation allows us to reconcile those results with recent observations of evolution in the first months on ART. Consequentially for the field of HIV cure, latent proliferation should be a target for curative therapies in concert with sustained ART.
A. Authors

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B. Title And Abstract

**Title:** Persistence criteria for the nonlocal niche model and applications

**Abstract:** Long range dispersal is a common phenomenon in biology and ecology. To have a better understanding of the evolution of biodiversity in some ecosystem, there is a need to understand the influence of nonlocal dispersals on the survival/persistence of a population.

In this talk, I will report on a recent study concerning persistence criteria in some nonlocal models on temporal and spatial heterogeneous environment. I will first present some spectral theory of the associated eigenvalue problem, such as the existence of the principal eigenvalue, and the asymptotic behaviors of the generalized principal eigenvalue with respect to its underlying parameters. As a consequence, I will discuss the applications of these results to the evolutionary invasion analysis. Secondly, I will show some results of the eigenvalue problem with indefinite weight functions, which have practical importance in the context of reserve design or pest control.
SMB 2017 Contributed Talk Abstract

Modelling on Coral Reefs Ecological System

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\textbf{Abstract:} Coral reefs are the most diverse of all marine ecosystems. They teem with life, with perhaps one quarter of all ocean species depending on reefs for food and shelter. The warmer water and more nutrients encourages the growth of harmful algae on top of the coral, which kills it, because it blocks out the sun. Without the sun, the zooxanthellae cannot perform photosynthesis and so they die. Without the zooxanthellae, the coral polyps die too. This algae is usually eaten by herbivorous fishes (parrotfish et al.), but because of over fishing, there aren’t enough fishes left to eat all the algae. In this talk, we focus on the fishing impacts on trophic cascades. We give several models to describe the interaction among algae, herbivorous fishes, carnivorous fishes and the fishing impacts, and then we study the dynamical behaviour of the given system.
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B. Title And Abstract

Title: Oscillations in epidemic models with spread of awareness

Abstract

This presentation reports joint work with Winfried Just and Joan Saldàna.

We study ODE models of epidemic spreading with a preventive behavioral response that is triggered by awareness of the infection. Previous studies of such models have mostly focused on the impact of the response on the initial growth of an outbreak and the existence and location of endemic equilibria. Here we study the question whether this type of response is sufficient to prevent future flare-ups from low endemic levels if awareness is assumed to decay over time. In the ODE context, such flare-ups would translate into sustained oscillations with significant amplitudes.

Our results show that such oscillations are ruled out in Susceptible-Aware-Infectious-Susceptible models with a single compartment of aware hosts, but can occur if we consider two distinct compartments of aware hosts who differ in their willingness to alert other susceptible hosts.
Group 6: Ecology and Evolution

A.

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B.

Numerical Methods on Irregular Domains for Animal Movement Models

Movement models to predict animal dispersal over time need to address heterogeneous landscapes with barriers, for example, shorelines for harbor seals and large rivers for mule deer. The ecological diffusion equation models random-walk population dispersal dependent on local habitat type. The telegrapher’s equation incorporates correlated movement choices and speed constraints. We adapt the Alternating Direction Implicit (ADI) method for efficient numerical solutions of these equations on irregular two-dimensional domains. We first consider simple domains such as L-shaped, and develop techniques for more complex boundaries such as ones following a coastline.
Competitive advantage of starvation driven diffusion on strong competition system

Wonhyung Choi (Presenter) \textsuperscript{1a} and Inkyung Ahn\textsuperscript{2b},

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Abstract

Starvation driven diffusion (SDD) is a dispersal strategy that increases the motility of biological organisms when they are in an unfavorable environment. The proposed model represents the interaction between two strongly competing species in a heterogeneous environment, which involves a Lotka-Volterra reaction. We show that the species with SDD has the competitive advantage. For example, the species that follows SDD can survive under the conditions that random diffusers cannot. Such competitive advantages are shown by investigating the stability of semi-trivial solutions of the system with SDD and comparing it to the conditions for the model with constant diffusion. The mathematical results will be expressed through numerical simulation.

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Testing Animal Motility Estimation Methods Using Simulations

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. With simulated landscapes and animal movement paths we test these methods. Motilities can then be incorporated into spatial models dealing with invasive spread, spread of disease, habitat use or population dynamics.
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2 Title and Abstract

2.1 Title:
The impacts of ecosystem engineering and sea-level rise on spread of invasions

2.2 Abstract

Ecosystem engineers are species capable of modifying their environment, changing the availability of physical or environmental resources for species living in that habitat. The ability to modify their environment can increase the spread rate of some invasive ecosystem engineers. *Spartina alterniflora*, a salt marsh grass that has invaded several regions along the Pacific coast, is an invasive ecosystem engineer that is capable of increasing the height of sediment above average tidal height. If *Spartina* increases sediment levels towards the optimal sediment height for reproduction, its ability to act as an ecosystem engineer increases its reproductive rate. As the average tidal height increases via sea-level rise, relative sediment levels will decrease, which will affect the distribution of habitat of varying sediment heights and the spread rates of *Spartina*. We develop and numerically analyze an integrodifference equation model of the spread of an invader capable of ecosystem engineering, in an environment heterogeneous in sediment level, subject to a constant amount of sea-level rise each generation.
**SMB 2017 Poster Abstract**

**A. Authors:**
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**B. Title:** How Competing Causes of Cellular Damage Shape the Evolution of Aging

**Abstract:** Evolutionary theories of aging (antagonistic pleiotropy and the disposable soma) were developed before the pathophysiology of aging was characterized. It is hypothesized that stochastic cell damage processes play a large role in causing the tissue damage associated with aging. I’ve developed a stage-structured ODE model that links cell and tissue damage with biological fitness in order to study how cell dynamics (death, division, and replacement) and their costs affect an organism’s life history.
A. Authors

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\textsuperscript{2}Presenter

B. Title and Abstract

Associational Resistance and Optimal Foraging

Evidence shows that plants are more strongly protected than their individual defenses (such as secondary metabolites and physical barriers) would suggest. One explanation is that in defending themselves, plants may also offer protection to their neighbors. In this work, we study this associational resistance by considering a system of two plant types and two insect types in a patch environment. Each plant type is specifically defended against one of the insect types, but only indirectly defended against the other insect type by the defenses of its neighbors. Defense-dependent insect behavior such as searching, choosing a plant, leaving plants or patches, and emigrating from the whole system is modeled by the marginal value theorem. We will explore optimal strategies for the insects, constrained by the structure of their plant hosts’ associational resistance. Under the assumption that insects behave optimally, we will examine how diversity in defense within a plant community affects herbivore load and plant damage.
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Title: Comparing optimal and feedback control of the yellow fever mosquito (A. aegypti)

Abstract: The yellow fever mosquito, Aedes aegypti, is well known for its role as a vector for tropical fevers including dengue and Zika, and, as such, is often the target for control efforts. We use a discrete-time stage-structured population model of the mosquito, controlled using malathion. We present and compare two control methods. Optimal control minimizes a cost, but might not be effective in the presence of uncertainties and perturbations. Adaptive feedback control can be robust to uncertainties and perturbations, but does not minimize cost, and has additional costs of monitoring the system. We compare the costs and robustness of these two strategies.
Artificial selection for dispersal in experimental metapopulations of *Tribolium*

In metapopulations, dispersal connects subpopulations residing in discrete patches of habitat surrounded by uninhabitable matrix. In the 1970s Levins showed that metapopulation persistence requires that colonization rates equal extinction rates, which in turn requires adequate dispersal. Dispersal rate, on the other hand, is determined by evolutionary forces acting on individual fitness, not population persistence. The dynamics of this interplay are not entirely understood. Any experimental study of such dynamics requires a species in which dispersal has high heritability. Here we investigate the heritability of dispersal in artificial metapopulations of confused flour beetles (*Tribolium confusum*). We show that dispersal in *T. confusum* has a strong heritable component, but also exhibits a high degree of plasticity depending on environmental conditions. The key environmental determinant appears to be humidity. We also corroborate the results of Ogden and others who suggest that dispersal can be artificially selected in this species, which also supports the conclusion of high heritability of dispersal behavior.
SMB 2017 Poster Abstract

A.

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B.

Human behavior change in terms of the addictive behaviors

Abstract

According to W.R. Miller, the addictive behaviors of individuals can become addicted, dependent, or compulsively obsessed with any activity, object, substance or behavior that gives their pleasure. A kind of behaviors are such as alcohol and psychological dependence involved in such activities as compulsive gambling, sex, work, or running. Thus we consider the human behavior to the addictive behaviors because of behavioral changes. That is, human behavior changes are driven by response to the action of others. In this point of view, we considered behavior addiction dynamical system from human behavior, and analyzed a mathematical model.

Key words: human behavior; imitation dynamics; evolutionary game dynamics;
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B. Title: Competing Barnacle species with time dependent reproduction rate.

Abstract:
Invasive species are regarded as a major threat to native ecosystems ([1], [2], [3], [4]), with their presence being associated with lower abundances of native species, changes in native ecosystem structure and decreased biodiversity ([1]). Barnacle species that live in the intertidal zone make ideal study organisms as they are easily accessible, are present in high densities and are easily manipulated. Using a cold water adapted native and a warm water adapted invasive barnacle species as model organisms we study the colonization of space by barnacle species with different life history traits in communities where the species are initially present at different densities and analyze the model behavior.

We provide a short discussion of the monotonicity property and speculation on the fact that our model is indeed monotonic in the prescribed sense showing the independence of the long-time evolution on the initial conditions. We show that the crucial factor of the described dynamics consists in the interplay between two dimensionless parameters: the ratio $k$ between the mean total amounts of the settled larvae for the native and invasive species and the delay $c$ between the peaks of the reproduction profiles related to the one-year period. In particular we derived the conditions of the coexistence of two barnacle species. The colonization of a novel substrate is also modeled in addition to colonization of space under the scenario of future climate change.

References:
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B. Title And Abstract

Title: A Juvenile-Adult Model for an Amphibian Population with Distributed Birth and Metamorphosis Rates

Abstract: A mathematical model of an amphibian population is developed where individuals are divided into two stages as juveniles and adults. Juveniles may be recruited into the population at different sizes and may metamorphose to adults with distributed states. We investigate how different birth and metamorphosis distributions affect the population dynamics. We further fit a set of green tree frog population estimates obtained from capture-mark-recapture field data to the model to gain understanding of the dynamic of the population.
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Title:

Invasion by competing types in a discrete heterogeneous habitat

Abstract:

We model a co-invasion by two competing, asexually reproducing genotypes in a one-dimensional lattice where the growth rates for the two types vary periodically. Numerical simulations allow us to describe how the wave speed depends on the ratio of the lengths of the two environments that make up the periodic habitat, as well as on the rates of reproduction of each type in each environment. We also describe how the wave speed approaches a limiting value as the lattice density increases toward the continuum limit. Our findings contribute to understanding of invasions in heterogeneous environments; they also represent a first step toward incorporation of genetic variability into models of invasion in patchy habitats.
PS71
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Title:
When to expect predator-prey coevolutionary arms races

Abstract:
Much of evolution is coevolution and classic examples of "coevolutionary arms races," such as tight predator-prey coevolution may be rare. Predators typically drive prey evolution, but prey only drive predator evolution under certain circumstances such as lack of alternative prey. By examining variation in prey availability (prey-switching probability) and substitutability (relative prey quality) in simulations of predator and prey populations through multiple generations and tracking trait change we can see the coevolutionary dynamics. Focal prey evolve from predator influence under all parameter scenarios. The predators evolve under most parameters except when alternative prey is abundant and substitutable. We hypothesize that tight coevolutionary arms races occur when alternative prey is rare and lower quality relative to focal prey and we seek to discover the points at which prey availability and substitutability change the arms race dynamic. Results have proven our hypothesis; the ratio between the trait change of the predator and the trait change in the prey, or "tightness" of the arms race, tends to be determined by both quality of alternative prey and prey-switching behavior of the predator. The tightest coevolution occurs when alternative prey abundance is low and its relative quality is low. As abundance of alternative prey increases the change in the predators capture trait will decelerate, loosening the race. By including trade-offs of escape/capture ability and reproduction there may be even more dynamics to explore and discovery of a range in parameter space that prevents arms races.
Group 7: Education

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Title and Abstract
A “Rule-of-Five” Framework for Models & Modeling to Improve Student Learning

Despite widespread calls for the incorporation of more quantitative skills, such as mathematical modeling, into the undergraduate biology curriculum, such integration remains limited. One barrier to this integration is the common understanding of modeling in terms of mathematical formalism, which inhibits communication between disciplines and provides a starting point for modeling that fails to match the background of the typical biology student. In this paper, we extend the “Rule of Four,” initially used in calculus reform efforts, to a framework that explicitly identifies five complementary representations of models and defines modeling activities as processes that relate pairs of representations. We show how this framework can be used to describe modeling activities engaged in by students and draw distinctions between modeling activities and other activities related to modeling that students do on a regular basis. Examples illustrate how the different modeling activities can be combined into a nuanced study of a model. Finally, we outline how the framework can be implemented to improve student-learning outcomes.
PS72a
Area: Pharmacology & Systems Biology

Mathematical modeling and analysis using MATLAB and SimBiology to support drug development

Fulden Buyukozturk\textsuperscript{1,*}, Christina Friedrich\textsuperscript{2}

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The average cost to develop one new approved drug has increased from $1 billion to $2.6 billion within a decade. A key driver of this increase is the high failure rates (88\%) for drugs in early phase clinical studies [1]. The use of models such as quantitative systems pharmacology (QSP) models that quantitatively describe dynamic interactions between a drug and disease pathophysiology with an aim to understand the system as a whole is gaining popularity in drug discovery and development [2]. The utilization of such models aims to improve understanding of the biological system, facilitate early and more thorough \textit{in silico} testing of drug candidates, and support rational decision making to reduce development cost and time.

Growing adoption of systems modeling approaches in drug discovery and development necessitate flexible and extensible computational tools. These complex disease physiology models are used to run often computationally-intensive simulations to answer questions such as on target feasibility, dose optimization, and impact of biological variance on efficacy and safety. To support these needs, computational tools should facilitate efficient construction and automation of such analyses. To this end, we present SimBiology, a MATLAB toolbox, as a flexible and extensible tool to streamline systems modeling and analysis in drug discovery and development.

We present the application of SimBiology and MATLAB to systems modeling in drug discovery and development with a rheumatoid arthritis (RA) case study [3]. SimBiology includes functions and capabilities to perform common tasks in systems modeling, such as simulation to predict system behavior, sensitivity analysis to identify significant biological pathways, and parameter estimation to fit models to data. We show the utility of SimBiology in exploring the potential of a combination therapy approach to improve clinical response to RA therapy. Using the RA case study, we demonstrate key features such as using sensitivity analysis to identify key pathways/parameters and running \textit{in silico} experiments to investigate the effect of mechanistic differences in pathophysiology on response to therapy. We also show how these simulations can be run in parallel on multicorees or on clusters for improved performance.

References:

3. Rheumatoid Arthritis (RA) PhysioPD™ Platform developed by Rosa & Co LLC.
Group 8: Epidemiology

A **Authors:** Andrew J. Basinski (presenter), Scott L. Nuismer, Tanner J. Varrelman, Mark Smithson, Ryan H. May, Christopher H. Remien

B **Title:** The use of transmissible, vectored vaccines in disease management

**Abstract:** Transmissible vaccines have the potential to revolutionize disease control by reducing the vaccination effort required to protect a population against a pathogen. Recombinant vectored vaccines are especially promising because they are built from benign vector organisms that pose little risk should the vaccine revert to its vector form; however, the shared antigenicity of the vaccine and vector may confer vaccine-immunity to organisms that have been previously infected by the vector, reducing the ability of the vaccine to spread through the population autonomously. Little is known about how vaccine and vector properties such as transmissibility and cross-immunity influence the effectiveness of such a vaccine in controlling a pathogen. We will present a mathematical model to quantify the efficacy of a recombinant vector vaccine, as it varies with transmissibility and cross-immunity with its vector. Results indicate that even with substantial cross-immunity between the vaccine and vector, recombinant vector vaccines can drastically reduce the vaccination effort required to control or eradicate a pathogen.
SMB2017 Poster Abstract

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B. Title:: Optimal Intervention Strategies for the Spread of Obesity

Abstract

The objection of the manuscript aim is to help reducing obesity or overweight. Since overweight and obesity are major risk factors for a number of chronic diseases, we would like to find the numerical results which effective control strategy minimize spread of obesity. Therefore, we hope the people do healthy lifestyle. We used as the numerical technique.

Numerical results indicated the effects of the two controls (prevention and education/campaigning) to be different. In societies with lower obesity, the social contact rate with the overweight and obese population play more prominent role in spreading obesity than lack of educational programs/campaigns. However, for societies with very high obesity burden, education/campaigning proved to be highly effective strategies.

Notwithstanding the efficacy and sophistication of the mathematics, reducing the social contact rate can result in other results such as a depression as well as an invasion of their individual rights. Therefore, the appropriate approach to obesity needed for lower obese societies. It is important to consider the program that works best with diet and the other social system.
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B. Title and Abstract
Staged Progression and Retrogression Model of Influenza

There have been many different variations of the SIR model developed by Kermack and McKendrick (1927). One such variation, the staged progression model presented by Hyman et al. (1999), is often used to model diseases such as HIV/AIDS that progress through multiple stages of infection. The presented model extends the staged progression model to include a retrogression pathway. Standard analysis for a disease model is performed and a conjecture for the basic reproduction number is made. As a case study, we study influenza dynamics using the progression-retrogression framework together with data from the HIVE study at the University of Michigan.
SMB 2017  Poster Abstract

A. Authors: Clayton A. Grubb\textsuperscript{1*} (presenter), Ryan S. Maziarz\textsuperscript{2}, Michele V. Moreno\textsuperscript{1}, Chandler Grant\textsuperscript{1}, Aleesa Monaco\textsuperscript{3}, Nicholas Roberts\textsuperscript{4}, and John D. Nagy\textsuperscript{1,4,\dagger}

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B. Title & Abstract

Title: A novel mathematical model of HIV and malaria epidemiology

Abstract:

Malaria and HIV are two of the most significant infectious diseases in the world today. Both diseases co-occur throughout much of their geographical ranges, particularly in sub-Saharan Africa. Although co-occurrence of malaria and HIV is frequently assumed to exacerbate their impact, this has not been studied in detail. Here we develop a mathematical model to investigate the epidemiology of these diseases and their interaction. Our model form is a semi-discrete-time dynamical system that includes population growth in the absence of disease; therefore, the model can apply to large (continent-scale) human populations in the long term. We apply the model to each disease in isolation to contrast their epidemic dynamics. We find that malaria prevalence is most sensitive to disease recovery rate, while HIV responds mainly to variations in disease-induced mortality. Additionally, HIV can become vanishingly rare but still persist within the population; however, this does not occur with malaria. Finally, we show that although no population endemic equilibrium exists, disease prevalence appears to always admit a simple attractor for both diseases.
A Authors

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B Title and Abstract

Estimating Disease Transmission Coupling from Spatio-Temporal Epidemic Data

Understanding the mechanisms by which infectious diseases are transmitted within and among human populations is essential to forecast the spread of epidemics and pandemics. Mathematical modeling provides many tools to understand disease spread, but estimating the degree of spatial coupling between populations is a difficult problem, because the contact process is not practically observable. We present probe-matching methods for estimating coupling among populations undergoing out-breaks, modelled as susceptible-infected-removed (SIR) systems. We test our methodology on mock observations from simulated epidemics. We apply our approach to weekly parish-level mortality data from the city of London, England, during the Great Plague of 1665–1666.
B) **Yield to the Resistance: The Impact of Nematode Resistant Varieties on Alfalfa Yield**

Alfalfa is a major cash crop in the western United States, where it is common to find fields that are infested with the alfalfa stem nematode (*Ditylenchus dipsaci*). With no nematicides available to control nematode spread, growers can use nematode resistant varieties of alfalfa to manage nematode populations in a field. I present a deterministic, discrete-time, host-parasite model that describes the spread of alfalfa stem nematodes on resistant hosts that was fit to experimental data obtained in Weber County, Utah. Numerical results obtained from simulations with the model are used to compare how varying levels of resistance can affect harvest yield. Results show that switching from a low resistant rating to a high resistant rating can approximately double the yield over the lifetime of the alfalfa crop.
Title: Impact of dengue infection on feeding behavior of *Aedes aegypti*

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Abstract:

Dengue viruses (DENV) are transmitted to humans by the bite of *Aedes* mosquitoes. It is known that dengue virus infection in *Aedes aegypti* female mosquitoes makes a change in the feeding behavior of the infected mosquitoes. In this study, using the forces of infection, we incorporated the effect of changes in the feeding behavior of mosquitoes into the standard vector-borne SIR-SI model. It has been proved that both a single-strain model and a two-strain model exhibit forward bifurcations. Moreover, optimal implementations of control with specific prevention measures for dengue transmission are analyzed. As a result we found that more implementation of controls on the secondary infection of humans should be considered for the behavioral changes in feeding of the infected mosquitoes.
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B. Title and Abstract
Mathematical model and control strategies for 2009 A/H1N1 influenza in Korea

Abstract
A mathematical model for the transmission dynamics of the 2009 A/H1N1 influenza epidemic in the Republic of Korea is developed. The simulation period is separated into three consecutive periods based on the government's intervention strategies: the nonpharmaceutical strategy is used during Period 1. The nonpharmaceutical and antiviral strategies are executed during Period 2 and the vaccine strategy is added during Period 3. During Period 1, we estimate the reduction in the transmission rate due to the government's intervention policies as a difference between the data-fitted and uncontrolled transmission rate that is derived from the basic reproductive number, $R_0$, of the model without intervention. This quantified reduced transmission rate is used as an upperbound of the nonpharmaceutical control for studying optimal control strategies, which is a new approach for determining the realistic upperbound of control. In this study, we also explore the real-time prediction of incidence using the mathematical model during the early stage of the epidemic. We investigate the impact of vaccination coverage and timing with respect to the cumulative incidence. The result implies that early vaccination plays a significant role for preventing the epidemic.
SMB 2017 Contributed Talk Abstract

A. Authors

Sungchan Kim\textsuperscript{a,1}, M. A. Masud\textsuperscript{b}, Giphil Cho\textsuperscript{a}, Il Hyo Jung\textsuperscript{a,2}
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B. Title And Abstract

Title
Analysis of a vector-bias effect in the spread of malaria between two different incidence areas

Abstract

Lacroix et al. (2005) demonstrated that infected humans are more attractive to mosquitoes, a phenomenon known as the vector-bias effect. The aim of this study was to determine how a vector-bias effect affects the changes in the dynamics of malaria transmission, and the changes in control strategies and cost-effectiveness for optimal control considering the regional characteristics or force of infections for different transmission rates. We used a vector-bias mathematical model and considered two different incidence areas: a high transmission area and a low transmission area. Our results showed that the dynamics in the two areas differed; as bias exists and the strategy for optimal control could be changed in the different areas. Thus, this work may give that considering the vector-bias effect in different areas facilitates prediction of the future dynamics and make decisions for establishing controls. We also mention the evolution of malaria parasites in this study.

References


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2017 Society for Mathematical Biology Annual Meeting Abstract Submission

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B. Title and Abstract
Title: The Role of HCWs in a Trade-off Model between Contact and Transmission for EVD.
Abstract: During 2014 in West Africa, the Ebola virus disease (EVD) became a serious public health concern where health care workers (HCWs) population suffered dramatically. EVD is transmittable by the movement of infected individuals, where infection is classified as asymptomatic or severe. Individuals with severe infections may be unable to move as much and therefore contacts with others will decrease. This involves a trade-off between contact and probability of transmission in the general population. In contrast, HCWs population do not experience the same trade-off, because as symptom severity becomes greater, contacts with HCWs will increase. A mathematical model was developed in order to interpret the effect of the trade-off by analyzing the basic reproductive number $R_0$ as a function of the probability of transmission. The main goal is to study this interesting twist and assess under what conditions HCWs become important drivers of transmission. It was found that $R_0$ in the model represents the contribution of both populations regarding EVD new cases. Moreover, parameter estimation of the model is performed for estimating the initial growth rate of an epidemic $r$ using the cumulative incidence data from the 2014 outbreak. Finally, $R_0$ was estimated from $r$ providing a match between the data, literature, and the deterministic model. This study could help to interpret how much the contribution in disease transmission from HCWs during the 2014 Ebola outbreak was, how fast EVD outbreak grew, and how to be prepared for another catastrophic outbreak with the necessary intervention capacity and adequate measurements for control.
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B. Title and abstract

Title: Co-infection dynamics in a novel model of HIV and malaria

HIV and malaria combined account for a large share of the effort and resources devoted to global health improvement. This is particularly apparent in sub-Saharan Africa, where the burden of both diseases can dominate daily life. While each disease on its own represents a significant health threat, their co-occurrence potentially exacerbates their combined impact. The precise nature of this interaction, however, is not fully characterized. Therefore, we developed a novel semi-discrete-time model to investigate the interaction between HIV and malaria in sub-Saharan Africa. Here we show that, in the absence of built-in physiological interaction between the two diseases, a population-level syndemic effect exists in which the presence of both diseases enhances their combined impact. Furthermore, HIV appears to be more responsive to physiological perturbation due to the presence of malaria than malaria is to HIV. Our results further the understanding of the co-infection dynamics of HIV and malaria and are pertinent to the ongoing effort to combat both diseases. In particular, we suggest that efforts to mitigate the effect of co-occurrence of these diseases should focus primarily on HIV intervention.
Ecology and Conservation biology

Do pathogens promote invasion of alien species?

Authors: Kengo Nagata¹, Yoh Iwasa²

Presentator: Kengo Nagata

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Abstract: Invasion of a foreign species can be promoted by being accompanied by a pathogen that infects both invaders and residents, if the pathogen was absent before the invasion. This is called disease-mediated invasion (DMI). For example, Polypedates leucomystax is a frog species native to Southeast Asia. P. leucomystax invaded to Japan after the world war 2, presumably accompanied by cargo, and now successfully invaded and chase away native frog species Rhacophorus viridis. Nematode parasites Raillietnema rhacophori discovered from Polypedates leucomystax was absent among R. viridis before the invasion of P. leucomystax. We study a simple model of two competitors, residents and invaders with their common pathogen enhancing mortality. Let $R_s$ and $P_s$ be the number of susceptibles, $R_i$ and $P_i$ be the number infected of residents and invaders, respectively. We focus on the condition in which the presence of common pathogen promotes the invasion success of the foreign species. When the initial population of invaders is very small, there are four outcomes: [1] the foreign species fails to invade and pathogen is not established among native species, [2] the pathogen can be established among native species but the foreign species failed to invade, [3] foreign species can invade and becomes coexist with the resident species, and [4] foreign species drives away the resident species. We derive mathematical conditions for these outcomes, and confirmed them by numerical analysis. Based on the mathematical analysis, we also discuss the case of invader frog P. leucomystax and resident frog Rhacophorus viridis and nematode pathogen R. rhacophori.
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B. Title: Tajima’s D & site-specific nucleotide frequency of pathogen during its outbreak

Abstract: Tajima’s D measures the selection pressure by calculating the difference between two estimates of genetic diversity in a given sample set of nucleic acid sequences, however, it is believed that Tajima’s D is biased by the population dynamics. Enormous sequence data of infectious disease pathogens have been accumulated so far, and Tajima’s D has been used for their analysis. To analyze the impact of population dynamics of infectious disease pathogen, which described by the standard SIR model on Tajima’s D, we developed an inductive algorithm for calculating the site-specific nucleotide frequencies from a standard multi-strain susceptible-infective-removed model (both deterministic and stochastic). We show that these frequencies are fully determined by the mutation rate and the initial condition of the frequencies. We prove that the sign of Tajima’s D is independent of the disease population dynamics in the deterministic model. We also show that the stochasticity in the transmission and evolution dynamics induces the dependency of Tajima’s D on the population dynamics of pathogens.
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B. Title And Abstract

Modeling the mitigation of Zika and dengue fever by infecting mosquitoes with Wolbachia

The ongoing mosquito-borne epidemics such as Zika virus and dengue fever have significantly affected human health and are of increasing concern worldwide. We develop and analyze an ordinary differential equation (ODE) model to assess the potential effectiveness of infecting mosquitoes with the Wolbachia bacteria, which is a natural parasitic microbe that stops the proliferation of the harmful viruses inside the mosquito and blocks the disease transmission. A sustainable release for the maternally transmitted Wolbachia bacteria in a wide mosquito population can be difficult due to the Wolbachia-induced fitness change and cytoplasmic incompatibility. Our model captures the complex vertical transmission cycle by including aquatic and adult life stages of mosquitoes as well as single and pregnant stages for female mosquitoes. We derive important dimensionless parameters and observe a critical threshold condition for a successful introduction of Wolbachia endemic: the infection will only persist if the fraction of the infected mosquitoes passes the threshold. This threshold effect is reflected by a backward bifurcation with three coexisting equilibria of the ODE system: a stable disease-free equilibrium, an unstable intermediate-infection endemic equilibrium and a stable high-infection endemic equilibrium. We also perform sensitivity analysis on epidemiological and environmental parameters to determine their relative importance to Wolbachia transmission and prevalence.
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Title and Abstract
Title: Using Cellular Automata to Model the Epidemic of Gun Violence in Chicago, IL
Abstract: Each year, gun violence leads to more than 31,000 deaths and 78,000 nonfatal injuries. Despite overall reductions nationwide since the 1990s, many cities still face staggering numbers of gun violence-induced deaths each year. In 2012, Chicago, IL, had the highest number of city-wide murders in the United States as a whole. Many refer to gun violence as an “epidemic,” spreading through a community similar to a communicable disease. We hypothesize that a cellular automata (CA) epidemic model can appropriately determine the underlying factors that lead to the spread of gun violence. A CA model consists of an array of cells, each existing in a defined state. Over time, the states update depending on local interactions with other cells. We simulate the spread of gun violence using tenets from SEIR epidemic models and spatially explicit CA models. This model can be used to uncover some of the factors leading to gun violence as well as predict future events. By determining the factors contributing to gun violence, we can better inform cities on how to control the spread of this epidemic.
Subject: SMB 2017 Poster Abstract

Filename: Shaier_Sagi.pdf

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Title:
The Effects of Domestic Animals on Human African Trypanosomiasis Transmission

Abstract:
The Human African Trypanosomiasis (HAT) parasite, which causes African Sleeping Sickness, is transmitted by the tsetse fly as a vector. It has several possible hosts, including wild and domestic animals, who are not as negatively impacted by the disease as the human host. It has long been assumed that because domestic animals can be a host for the parasite, that keeping domestic animals near human populations increases the spread of the disease. However, several parameters found in the literature, including the shorter lifespan of the male vector, and the female vector's preference for domestic animals, made us question this assumption. We developed a differential equation compartmental model to examine whether increasing the domestic animal population can be used to deflect the infection from humans, and reduce its impact. We found that the relationship between the number of domestic animals and the number of humans is not a simple one, and various (realistic) parameter values and initial conditions can result in the slowing of the spread of the disease, eliminating the disease, and even limit cycles in the infectious tsetse fly population.
A Multi-Group Model to Describe The Transmission of Healthcare-Associated Infections

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Abstract:

A Healthcare-Associated Infection (HCAI) is related with the use of some healthcare services. The name HCAI is more appropriated than Hospital-Acquired Infection because it involves all kinds of services, such as homecare. The most important class of service is the Intensive Care Unit (ICU), which regards more invasive procedures that increase the probability of such acquired infections.

Many microorganisms can cause the infection, which, in turn, is responsible for the increase in public healthcare costs, by increasing the internment time and mortality rate.

We proposed a multi-group model of Ordinary Differential Equations to describe the transmission of a HCAI throughout Brazilian Hospitals Network. In order to assess the dynamics we considered three different situations. The first one, where there is neither a connection between ICUs and nursing services nor among hospitals. The second one, where there is a connection between ICU and nursing services, but not among hospitals. Lastly we considered that there is a connection between ICU and nursing services as well as among hospitals.

We calculated the R0’s expression for all of those situations and we demonstrated that the connection between ICUs and nursing services can decrease the R0 in the hospitals as do the connection among hospitals. Lastly we performed some simulations in order to prove our results. We obtained information about the address and number of beds for 6221 hospitals in Brazil. All the information was acquired on the Brazilian Healthcare Ministry webpage. The simulations were done using a network built considering the hospital’s location and their sizes.
SMB 2017 Poster Abstract

A.

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B.

Optimal control strategies depending on interest level for the spread of rumor

Abstract

A variety of information diffuses quickly due to the development of various media such as social networks which can cause too many spreads of rumor. In this regard, we need to establish strategies for controlling the rumor. In this study, we propose rumor model with three control strategies for controlling the spread of rumor; 1) announcing the truth before ignorants receive rumor 2) punishing spreaders 3) deleting information about the rumor in media, and consider optimal control problems to minimize the number of spreaders while minimizing the cost of three control strategies for preventing the spreads of rumor. Analysis of optimal control problems is conducted via Pontryagin’s Maximum Principle. Furthermore, adapted optimal control is considered to investigate the effect of three controls under isoperimetric constraints. We analyze this problem by using Runge-Kutta method, Forward-Backward method, and Secant method. After we solve optimal control problems, numerical simulations result in various strategies for distributing controls depending on the initial value of spreaders and the interest level of rumor. The results imply that three controls are more effective to prevent the spread of a rumor when the initial value of spreader is lower, and quantity and timing each control is applied are different with the change of interest level.

Key words: Rumor model; Optimal control; Numerical simulation; Interest level; Isoperimetric constraint
Group 9: Fluids and Physiology

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Title and Abstract:

Sensitivity Analysis of a Cardiovascular-Respiratory System Model under Constant Workload

Parameters of a dynamical model are estimated by searching for those parameters in the parameter space which minimize the error of the model output to the experimental data. A fundamental question to ask is what parameters should be estimated. In this work, we perform sensitivity analysis on the parameters of a model for the cardiovascular-respiratory system under a constant ergonometric workload to identify parameters that are influential to the arterial systemic pressure, for which experimental data are available. We considered three different methods - traditional sensitivity analysis, partial rank correlation (PRC) and extended Fourier amplitude sensitivity test (eFAST) analysis. For each of the three methods, a ranking of parameters was obtained according to sensitivity. A set of five parameters with high sensitivities across the three methods was identified. A subset selection algorithm was also performed to determine how the chosen set of five parameters compares to other combinations of five parameters. Lastly, parameter estimation of the five identified parameters was performed on three different datasets. The resulting model output under the optimal parameters indicates a very good fit to the data.
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B. Title and abstract
Title: Modelling plant growth: what are the limitations to carbon allocation?
Abstract:
Improving crop yield is essential to meet increasing global food demands. Boosting crop yield requires the coordination of carbon acquisition by leaves and carbon utilisation by roots and seeds. Simple modelling approaches may be used to explain how this coordination is achieved within plant growth. Here, the limits to allocation strategies are explored by analysing the sensitivity of a simple root-shoot carbon allocation model. The model is formulated based on fundamental constraints on plant growth and therefore can be applied to all plants. This general approach shows that parameters defining the cost of root and leaf respiration alter the relationship between carbon allocation and final plant size by enabling a range of allocation strategies to produce a similar plant mass. This plasticity is enhanced by increasing assimilation rate and reduced by increasing the effect of shading within the model.
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B Title and Abstract

Title: Exploring the Effect of Membrane Curvature on Lipid Flow

Abstract: We develop a general model of a multicomponent membrane where we treat the membrane as a two phase viscous fluid flowing on a time dependent surface. We present the basic theory of differential geometry, and use it to describe the shape evolution of the membrane. Using Flory–Huggins–de Gennes theory combined with Cahn–Hilliard theory to describe the free energy of a mixture and Helfrich theory to describe the bending energy of a membrane, we use a minimum energy dissipation argument to derive equations of motion for the two phase fluid. By examining specific parametrizations of the surface, we explore situations under which the membrane undergoes phase separation, and demonstrate the possibility of curvature induced instability.
Optimizing Flow in Branching Lymphatic Vessels:

Understanding lymphatic development is clinically relevant in applications from the viability of embryos, to chronic inflammation, to cancer metastasis. I specifically address the branching of developing lymphatic vessels, and flow through these vessels. While branching in arterial development is understood to consistently follow Murray's Law, I have found that an optimization law for lymphatic vessels is less straightforward. Several of the assumptions necessary for Murray's Law do not hold, and Murray's Law itself does not hold. Rather, the relationship between the parent and daughter vessels is upheld through a strictly additive rule, and the parent vessels are larger than would be predicted by a radius-cubed law. The variability in vessel diameter and potential for backflow suggest a different optimization strategy based on the geometry and function of the system. Future work will consist of examining other models based on branching structure, flow, pressure, shear, vorticity, or efficiency, using the immersed boundary method.
Title: Cell swimming driven by cortical tension gradients

Abstract: Locomotion of cells, both individually and collectively, plays an important role in development, the immune response, and cancer metastasis. Some prokaryotes such as bacteria use flagella, while eukaryotes such as paramecia use cilia to swim, but both types can only use one mode. However other eukaryotes, such as tumor cells, are more flexible and can adopt the mode used to the environment in which they find themselves. For example, it has recently been found that some immune-system cells such as leukocytes can migrate through the fibrous extracellular matrix without the aid of integrins. Others such as Dictyostelium can swim by propagating protrusions along the cell length. Another mode of swimming is driven by a front-to-rear cortical flow observed in some recent experiments. These experiments suggested a new mechanism in which the cortical flow generates an axial cortical tension, which in turn generates a tension gradient in the membrane that leads to cell propulsion. Here we report that this mechanism can generate significant rates of cell movement, and thereby show that this is a potential mechanism to explain the recent experimental observations.
Abstract

**Background:** Vaccine-initiated immune activation is sufficient to prevent an infection of seasonal influenza in most individuals. However, there are cases of non-responders to vaccination due to immunosenescence or underlying host genetics. Response to vaccination can be measured by hemagglutination-inhibition (HAI) antibody titers at day-28 post-vaccination; however, to protect potential non-responders, models are needed that predict day-28 response from initial conditions. In order to understand and predict low immune response to vaccines, cellular models are well suited. These cellular models typically include important immune cell subsets, such as T cells and B cells. While data is readily available for the tracking and quantifying of antibody production by activated B cells (HAI), other cellular data is more difficult to obtain for inferring a complete cellular model. Gene expression, on the other hand, is routinely measured from the blood compartment and can be related to specific cell populations and may be used in place of cellular data in mathematical modeling to predict whether a given individual is a responder or a non-responder to a vaccine.

**Methods:** We propose a cellular mathematical model that incorporates expression levels of genes that are associated with the activity of T cells and B cells. We show that the genes associated with activity of T cells and B cells are those that exhibit significant variation correlated with fluctuation in activity of these cells. This will also allow us to predict varying levels of antibody production. Specifically, we model post-flu vaccination gene expression levels linked to the dynamics of CD8$^+$ T cells, B cells, and antibodies specific to common flu virus strains. We use next-generation sequence-based transcriptomic (RNA-Seq) data measured in influenza-vaccinated individuals at multiple time points (including baseline before vaccination) to train the model. We validate the mechanistic model’s ability to predict antibody production at day-28 from baseline gene expression levels.

**Conclusions:** With the predictive capability of selected genes, we will present expression dynamics associated with varying levels of responsiveness to the flu vaccine. This model will potentially provide early identification of individuals who are at risk to be unprotected from infection and may allow us to propose mechanisms for vaccine design to turn non-responders into responders. We will also present our estimates of model parameters obtained by fitting the model to time-series data for gene expression.
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Title
Mathematical model of hematopoietic system with myeloid bypass.

Abstract
Hematopoietic system is maintained by hematopoietic stem cells (HSCs) with dual abilities of long-term self-renewal and differentiation to all types of blood cells. Recently, using a single-cell transplantation system and mice expressing a fluorescent protein, myeloid-restricted progenitors with long-term repopulating activity (MyRPs) were found. Moreover, by using paired daughter cell assay, MyRPs were directly differentiated from HSCs.

In this study, we investigated hematopoietic system incorporating the novel insight that there existed a cell type that exclusively differentiated to myeloid lineages. There were five populations in the model: (i) long-term HSCs, (ii) short-term HSCs, (iii) MyRPs, (iv) myeloid cells, and (v) lymphoid cells. Myeloid cells were produced after transplantation of a single HSC via short-term HSCs or MyRPs, while lymphoid cells were produced via only short-term HSCs. This is the first study of investigating hematopoiesis with MyRPs. We estimated some parameters which were growth rate, production rate and death rate. Finally, we found that myeloid bypass plays an important role after transplantation.
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B. Title and Abstract
Title: Does Exhaustion Explain Low T-cell Functionality in the *Mycobacterium tuberculosis* Granuloma?

Abstract: Each year, approximately 2 million people die from Tuberculosis, an infectious disease caused by *Mycobacterium tuberculosis* (Mtb). The hallmark of Mtb infection are granulomas. These are a collection of host cells whose purpose is to contain or clear infection, creating a complex hub of immune and bacterial cell activity. Yet, given cellular activity and potential for frequent interactions between host and bacterial cells, a surprisingly low quantity of Mtb-responsive T cells (~ 8% of granuloma T cells) was observed in a recent study of Mtb infection within non-human primate (NHP) granulomas (Gideon et al. 2015).\(^1\) Various mechanisms could limit T cell function, one hypothesis is T cell exhaustion. While T cell exhaustion lacks a formal definition in the literature, continual antigen stimulation causes a subpopulation of T cells to enter a state characterized by low cytokine production, low proliferation and a series of inhibitory receptors – the most popular of which are PD1, TIM3, LAG3 and CTLA4 (Kahan, Wherry and Zajac 2015; Wherry 2011).\(^2,3\) In this work, we utilize experimental data to calibrate and inform an agent-based model (Ray et al. 2008; Segovia-Juarez et al. 2004)\(^4,5\) that captures environmental, cellular, and bacterial dynamics within granuloma formation in lungs during Mtb infection. Specifically, we updated a previous version of this model to evaluate the direct impact of an exhausted T cell phenotype. We compared results with a range of 5-95% exhaustion to predict the impact that T cell exhaustion would have on granuloma-scale outcomes. Together, the conclusions of our model coupled with the results of experimental work suggest that T cell exhaustion alone cannot be responsible for the low quantity of Mtb-responsive T cells found in granulomas.

A mathematical model explaining the effect of Raphanus Sativus on cancer diseases

There has been a recent spark of interest in identifying natural products that can be used as cost-effective alternative for cancer treatment. In particular, recent experiments confirm the effectiveness of *Raphanus Sativus* (*R. sativus*; more widely known as white radish) in fighting cancerous cells. However, the principle behind this positive result is not known due to lack of information on the possible interactions that can explain it. To understand the complexity of drug-disease dynamics, we have built the first mathematical model comprised of a set of nonlinear differential equations. The model describes a possible network that can mimic the experimentally obtained expression levels of cancer cells by elucidating the dynamic behavior of Cyclin D1-CDK protein, previously shown to be of vital importance for the cancer cell cycle. Based on our results, we have identified the candidate proteins targeted by *R. sativus*; which can be confirmed experimentally if the interaction network identified by the model is indeed responsible for the beneficial outcome of treating the cancer cells with *R. sativus*. 
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B. Title and Abstract

Title

“Multiscale modelling of drug transport in systems pharmacology”

Abstract

Multiscale mathematical modelling can provide the utility to extrapolate in vitro experimental data, obtained at a range of scales (genes, proteins, cells, tissues), to better understand drug toxicity at the organism scale, and thus inform personalised medicine. In vitro experiments in 2D culture, taken in isolation, tend to be poorly predictive of toxicity but emerging 3D systems are more physiologically relevant and predictive of the in vivo environment. The development of spatio-temporal data generated by 3D cell imaging offers tremendous opportunities for developing, parameterising and testing multiscale mathematical models and in response mathematical modelling can be successfully used to optimise these developing technologies. Furthermore, it is vital to integrate such optimised data within the mathematics in order to develop models for drug therapy with enhanced predictive potential. Examples of multiscale modelling research in systems biology and pharmacology will be presented that couple mechanistic modelling of biochemical transport kinetics and protein interactions at the cellular microscale with physical processes and structural elements at the macroscale, integrated with experimental data. The numerous mechanical and biochemical interactions involved when drugs enter biological systems result in highly complex modelling problems. However, multiscale modelling tools allow for appropriate averaging techniques to develop tractable models, identify key toxicity mechanisms and provide testable predictions which can be up-scaled to clinically relevant predictive models.
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B Title And Abstract

Title:
Modeling Antibody-Mucus-HIV Kinetics

Abstract:
Many viruses are able to move freely through mucus, yet mucus is an invaluable protective barrier. Experiments demonstrate that even a virus with absolutely no affinity to mucus can become trapped in a mucus network that also contains antibodies (Ab). Ab and mucus work cooperatively to trap viruses by forming an Ab-virus attachment on one end the Ab and an Ab-mucus attachment on the other end, anchoring the virus to the mucus via the Ab attachments. Our research models the attachment/detachment of Ab as HIV move through mucus, generating many unexpected yet important insights into the design of antibodies, and offering a promising strategy for protection against the male to female transmission of HIV.