# Book of Abstracts

of the

Society for Mathematical Biology

Annual Meeting and Conference

Knoxville, Tennessee

July 25-28, 2012

Theme:

Mathematics and Biology:

Interdisciplinary Connections and Living Systems

Hosts:

National Institute for Mathematical and Biological Synthesis

and

University of Tennessee

# SMB 2012 Author Index - alphabetical by presenting author

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This is a joint work with Prof. Suzanne Lenhart and Prof. Huaiping Zhu

## Optimal Control of West Nile virus in mosquito, birds and humans with Season

In Canada the number of West Nile virus (WNv) infection of humans decreasing during the years of 2007-2010. However, it started increasing once more during last year 2011 despite the immense efforts exhibited by the specialized agencies to control the vector mosquitoes and the disease. In this study, we use mathematical models to study the behavior of the transmission of WNv in the mosquito-bird cycle and human (considering two kinds of birds: corvids and non-corvids). We study and compare the mathematical model of WNv without the effect of the seasonal variation and the modified model with seasonal variations. Firstly, we proved that the autonomous model undergoes a backward bifurcation. Secondly, we extended the model by adding three control functions: adulticide, larvicide and human protection. We simulated a set of possible control strategies and conclude that: (1) The feasibility of controlling WNv could be dependent on the initial sizes of the sub-population when we have a backward bifurcation. (2) Combining adulticide and larvicide is the most effective strategy to control an ongoing epidemic (in reducing disease cost). (3) The results further emphasized the importance to use the information about quantity of other animals infected and the percentage of the non-corvids bird at any region before applied the control strategies. (4) With impact of the seasonality identifying the ultimate time of adulticide and larvicide (individually and grouped) to achieve the best control strategy. Our findings emphasize the importance of carefully taking into account the impact of the seasonal variation when we applying the control.

# Rich dynamics in multi-strain models: non-linear dynamics and deterministic chaos in dengue fever epidemiology

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March 21, 2012

**Abstract**

Dengue fever is a viral mosquito-borne infection, a major international public health concern with more than 55% of the world population at risk of acquiring the infection. Two variants of the disease exist: dengue fever (DF), a non-fatal form of illness, and dengue hemorrhagic fever (DHF), which may evolve toward a severe form known as dengue shock syndrome (DSS). Epidemiological studies support the association of DHF with secondary dengue infection due to a process described as antibody-dependent enhancement (ADE), where the pre-existing antibodies to previous dengue infection cannot neutralize but rather enhance the new infection. Treatment of uncomplicated dengue cases is only supportive, and severe dengue cases require hospitalization and proactive treatment of hemorrhagic symptoms. A vaccine against dengue is not yet available, although several candidates of vaccines are at various stages of development.

Dengue epidemiology dynamics is well known to be particularly complex with large fluctuations of disease incidences and mathematical models describing the transmission of dengue viruses appeared in the literature as early as 1970. To capture differences in primary and secondary dengue infections, a two-strain SIR-type model for the host population has to be considered. Dengue models including multi-strain interactions via ADE, but without temporary cross-immunity, have shown already deterministic chaos when strong infectivity on secondary infection was assumed. The addition of the temporary cross-immunity peri- od in such models brings a new chaotic attractor in wider and unexpected parameter region.

In this talk we present different extensions of the classical single-strain SIR model motivated by modeling dengue fever epidemiology with its peculiar ADE phenomenology. We focus on a minimalistic model, where the notion of at least two different strains is needed to describe differences between primary (DF) and secondary dengue infections (DHF). The model, in its simplicity, has shown qualitatively very good results when comparing empirical DHF data and model simulation, offering a promising perspective on inference of parameter values from dengue case notifications. A model which can be fully parametrized on data referring to incidence of disease can become a predictive tool to guide the policies of prevention and control of the dengue virus transmission, including the implementation of vaccination programs when the candidate dengue fever vaccines will be available.

**Folashade B. Agusto**

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## Malaria Drug Resistance: The impact of Human Movement and Spatial Heterogeneity

Human habitat connectivity, movement rates and spatial heterogeneity have tremendous impact on the effectiveness of malaria control and eradication. In this paper, a deterministic system of differential equations for malaria transmission in a two patch system that incorporates human movements and the development of drug resistance malaria is presented. The impact of movement between the patches is determined by qualitative analysis of the model basic reproduction number. Sensitivity analysis is performed on the key parameters that drive the disease dynamics of the model in order to determine their relative importance to disease transmission and control within and between patch.

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## An Epidemic Model with Age of Infection-Dependent Transmission Rate and Waning Immunity

The aim of this work is to provide a model for infectious agents with a transmission rate that varies during the infectious period, and/or that have the ability to reinfect a host.

Influenza is an example of a disease that satisfies both characteristics. The probability that an individual transmits influenza is directly related to the amount of virus shedding, which is linked to the time that has elapsed since the individual became infected (age of infection). The infectivity reaches its peak after 2-3 days then decreases until the person recovers. In addition to that, being infected with influenza completely protects the individual against reinfection by the same strain. But the virus mutates via the process known as drift, and new strains, against which the individual only has partial protection, appear in the population. Without the introduction of a completely new strain in the population (a shift process occurring) the immunity of a host to reinfection depends mainly on the amount of time that has elapsed since his last infection.

A nonlinear age of infection-dependent epidemiological model is proposed. Conditions for the existence, positivity, regularity and continuity of the solutions will be addressed. The analysis of the existence and stability of equilibrium solutions will be conducted using the theory of strongly continuous nonlinear semigroups. The model exhibits interesting outcomes, including the existence of multiple endemic equilibria, a backward bifurcation (i.e., the existence of a stable endemic equilibrium with $R_0 < 1$), and the existence of a stable endemic equilibrium even in the absence of vital dynamics.

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## Polymerization-driven, adhesion-mediated actin traveling waves in motile cells

Traveling waves in actin have received much attention recently. Fish keratocyte cells, which usually exhibit rapid and steady motility, exhibit traveling waves of protrusion when plated on highly adhesive surfaces. Protrusion speed correlates strongly with wave propagation speed but not with retrograde flow. Mature adhesions co-localize with transiently stalled parts of the leading edge, while F-actin density is elevated in the protruding parts. We hypothesize that waving arises from a competition between actin polymerization and mature adhesions for VASP, a protein that associates with growing actin barbed ends. We developed a mathematical model of actin protrusion coupled with membrane tension, adhesions and VASP. The model is formulated as a system of partial differential equations with a nonlocal integral term and noise. Simulations of this model lead to a number of predictions, for example, that overexpression of VASP prevents waving, but depletion of VASP does not increase the fraction of cells that wave. The model also predicts that VASP exhibits a traveling wave whose peak is out of phase with the F-actin wave. Further experiments confirmed these predictions and provided quantitative data to estimate the model parameters. We thus conclude that the waves are the result of competition between actin and adhesions for VASP, rather than a regulatory biochemical oscillator or mechanical tag-of-war. We hypothesize that this waving behavior contributes to adaptation of cell motility mechanisms to perturbed environments.

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## Stochastic Inference of Cell Migration Phenotypes

Cell migration requires precise spatiotemporal regulation of the actin cytoskeleton. Key regulators of cell movement are the Rho family of GTPases. Experimental data and computational models have described the role of the Rho GTPases Rac1, Cdc42 and RhoA in cell polarization and migration.

To investigate the role of RhoG, a Rac-like Rho GTPase, in cell migration, we developed computational tools, based on stochastic modeling, to analyze time series data for the position of randomly migrating cells. Our approach allows parameters that quantitatively characterize cell movement to be efficiently estimated from experimental data. This feature revealed that randomly migrating cells stochastically transition between distinct states of migration characterized by differences in cell speed and persistence.

The predicted states are shown to correlate with differences in the spatiotemporal activity of the Rho family members Rac1 and RhoG. We have also shown that RhoG is actively transported to the leading edge of migrating cells, and this approach has shown that without RhoG the locations of Rac1 activity are less spatiotemporally dynamic leading to an increase in persistence in this case. This leads us to hypothesize that RhoG is required to hasten formation of localized regions of Rac1 activity, and by this mechanism RhoG can regulate turning in randomly migrating cells.

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## Interference competition and invasion: spatial structure, novel weapons and resistance zones

Certain invasive plants may rely on interference mechanisms (e.g., allelopathy) to gain competitive superiority over native species. But expending resources on interference presumably exacts a cost in another life-history trait, so that the significance of interference competition for invasion ecology remains uncertain. We model ecological invasion when combined effects of preemptive and interference competition govern interactions at the neighborhood scale. We consider three cases. Under "novel weapons" only the initially rare invader exercises interference. For "resistance zones" only the resident species interferes, and finally we take both species as interference competitors. Interference increases the other species' mortality, opening space for colonization. However, a species exercising greater interference has reduced propagation, which can hinder its colonization of open sites. We analyze invasibility criteria of both a mean-field (homogenous mixing) and a pair approximation, and apply these results to interpret simulations of the full spatial model.

Interference never enhances a rare invader's growth in the homogeneous mixing approximation to our model. But interference can significantly increase an invader's competitiveness, and its growth when rare, if interactions are structured spatially. That is, interference can increase an invader's success when colonization of open sites depends on local, rather than global, species densities. In contrast, interference enhances the common, resident species' resistance to invasion independently of spatial structure, unless the propagation-cost is too great. The particular combination of propagation and interference producing the strongest biotic resistance in a resident species depends on the shape of the tradeoff between the two traits. Increases in background mortality (i.e., mortality not due to interference) always reduces the effectiveness of interference competition.

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## Genetic vector control strategies to reduce the burden of mosquito-borne diseases

Vector-borne diseases impose enormous health and economic burdens and additional methods to control vector populations are clearly needed. The Sterile Insect Technique (SIT) is an area-wide method of biological pest control whereby large numbers of a pest insect are bred, sterilized (currently by irradiation) and then released. The sterile insects mate with wild insects, but no viable offspring result from those matings. The SIT has been successful against agricultural pests, but is not in large-scale use for suppressing or eliminating populations of mosquito disease vectors. Genetic RIDL® technology (Release of Insects carrying a Dominant Lethal)* is a modification that involves releasing insects that are homozygous for a repressible dominant lethal genetic construct rather than being sterilized by irradiation, and could potentially overcome some technical difficulties with the conventional SIT technology. Field trials in *Aedes aegypti*, the principal vector of the arbovirus dengue, are ongoing.

Using dengue as an example, we combine vector population dynamics and epidemiological models to explore the effect of a programme of RIDL releases on disease transmission. We use these to derive a preliminary estimate of the potential cost-effectiveness of vector control by applying estimates of the costs of SIT. Through mathematical modelling, we predict that this genetic control strategy could eliminate dengue from a human community in a timescale within one year, and at lower cost than the direct and indirect costs of disease that would be averted by doing so.

The theoretical framework has wider potential use; by appropriately adapting or replacing each component of the framework (entomological, epidemiological, vector control bio-economics and health economics), it could be applied to other vector-borne diseases or vector control strategies and extended to include other health interventions.

* RIDL® is a registered trademark of Oxitec Limited, UK.

**Melissa Anthony**, Saint Louis University, St. Louis, MO, USA

Daryl Trumbo, Washington State University, Pullman, WA, USA

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## Spatial Autocorrelation in Species Distribution Models: Simultaneous Incorporation of Multiple Scales of Influence Using a Bayesian Framework

Spatial autocorrelation (SAC), defined as the positive association between sample similarity and spatial proximity, is pervasive in ecological data. Several methods exist for the incorporation of SAC into statistical models, but not until recently have these methods been applied to species distribution data. When incorporated into species distribution models, SAC has been found to significantly alter model coefficients, subsequently changing the statistical inference of the model. Models without a SAC component run the risk of overestimating the relationship between environmental variables and the presence or abundance of a species, potentially resulting in poor predictive ability of the model. Numerous studies have demonstrated the improvement in species distribution model performance after the incorporation of SAC suggesting inclusion of this spatial component is essential for developing statistical models that accurately predict species distributions in novel environments.

All methods of incorporating SAC into species distribution models operate by scaling the probability that a species is present in one location by the probability that the species is present in nearby locations. Many of these methods only quantify SAC on a single scale resulting in models that lack the ability to take into account how SAC may affect the parameter estimates of environmental variables across different spatial scales. For example, climate varies on a larger geographic scale than variables such as soil or vegetation type, and the effect of SAC when determining the relative ability of these variables to explain a species' distribution should be scaled accordingly. This study attempts to address this scaling issue by using Bayesian additive models which incorporate SAC in the form of a spatial random effects parameter specified by a Gaussian conditional autoregressive model. The use of additive models allows the inclusion of a separate spatial random effects parameter for each scale of SAC present in the model as dictated by the scales of the environmental variables. For example, the spatial random effects coefficient when modeling the association between climate and species presence will be estimated using samples over a larger geographic distribution than more local measurements of the environment, such as vegetation type. By correctly partitioning the variation in observed species presence between the environment and the appropriate scale of influence, species distribution models are expected to exhibit higher performance and predictive power.

Another weakness of current methods of incorporating SAC into species distribution models is the frequentist approach to model parameterization, which does not appropriately quantify model uncertainty. Species distribution models that are built using data from a relatively small geographic range are often extrapolated to make predictions over larger areas. Accurate quantification of the uncertainly of model predictions is crucial in conservation planning and failure to do so can hinder the decision making process. This problem is addressed in the current study by using Bayesian methods of model parameterization that incorporate the uncertainly of model parameters in making predictions, unlike frequentist methods which make predictions based solely on a single value for each parameter.

To investigate how this new strategy performs, data are used from a survey of 103 ponds sampled for six amphibian species along with corresponding abiotic data that represents the environment at multiple scales. Model performance will be assessed and compared to other commonly used methods to quantify the improvement in predicting species distributions.

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**Modeling a time-area closure as a tool for managing US tuna fisheries**

We analyze a multispecies, multifishery bioeconomic model of US tuna fisheries. Specifically, we examine conditions for which implementing a time-area closure would increase the economic value of fisheries, focusing on a case study application in the Gulf of Mexico. Pelagic longline fishermen catch the highly valued Atlantic bluefin tuna (Thunnus thynnus, Scombridae) on their Gulf of Mexico spawning grounds while fishing for Atlantic yellowfin tuna (Thunnus albacares). We identify management strategies that would maximize the net present value of tuna fisheries, allowing for discounting of future benefits and costs relative to the present. If past fishing mortality rates continue in Atlantic bluefin tuna fisheries, implementing a time-area closure in the Gulf of Mexico incurs economic costs. However, the net present value of the fisheries is increased by implementing a time-area closure as part of a broader commitment to rebuild the heavily depleted bluefin population, provided the discount rate and the costs of such a closure in forgone fishing opportunities are not too large.

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## Optimal reproductive strategy for the fire ant (*Solenopsis invicta*) over multiple seasons

In ant species, the queen ant spends her life mostly by laying eggs and the sterile workers forage, take care of the queen and broods, and defend their nest from predators. The queen of the fire ant (*Solenopsis invicta*) mates only once at the beginning of her reproductive life. She produces offspring (sterile workers and sexuals) until she uses up the sperm which she initially received. In the field, typical lifespan of queen is about 6 - 7 years although some may live much longer.

In our model, monogyne form of the fire ant colony is considered. We formulate and analyze a model using a system of differential equations to study the optimal resource allocation strategies over multiple seasons under different scenarios including seasonal variation in resource availability.

**Austin Baird**, University of North Carolina, Chapel Hill, USA
Laura Miller, University of North Carolina, Chapel Hill, USA

## Pumping Mechanism of the Tubular Sea Squirt Heart

Tubular valveless hearts are common in many invertebrates, such as Drosophilia or Ciona, and are also found in the early stages of vertebrate cardiac morphogenesis. This diversity of hearts motivates the question of how scaling affects fluid transport for several mechanisms of valveless pumping. Physical and numerical models are used to quantify pumping efficiency as a function of Womersley number for peristalsis and dynamic suction pumping.

## Experimental Design for Vector Output Systems

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### Abstract

We formulate an optimal design problem for the selection of best states to observe and optimal sampling times for parameter estimation or inverse problems involving complex nonlinear dynamical systems. An iterative algorithm for implementation of the resulting methodology is proposed. Its use and efficacy is illustrated on two applied problems of practical interest: (i) dynamic models of HIV progression and (ii) modeling of the Calvin cycle in plant metabolism and growth.

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## Protein Electrostatics on a Desktop Using GPU Hardware and Multipole Algorithms

When studying the electrostatic interactions of molecules in solution, Poisson-Boltzmann solvers are a popular alternative to molecular dynamics. Among these solvers, the boundary element method (BEM) has become a competitive choice, compared to volume-based methods (finite difference, finite element). In BEM, the partial differential equation is formulated as a boundary integral problem for surface charge on the molecule-solvent interface, giving rise to a linear system. One disadvantage of BEM formulations is the generation of dense matrices, resulting in $O(N^2)$ complexity due to matrix-vector multiplications within iterative solvers. This precludes using more than a few thousand elements, which limits the accuracy that can be obtained with complex geometries, where finer discretizations are required. To obtain BEM solutions of large molecules, a fast algorithm for performing the dense matrix-vector multiplications is required. Treecodes or fast multipole methods have been used to reduce the complexity from $O(N^2)$ to $O(N \log N)$ or $O(N)$, respectively. Combining these fast algorithms with the latest GPU hardware, desktop calculations of protein electrostatics become practical even for large molecules.

Although we have previously developed high-performance tools for multipole-based algorithms on GPU clusters, in this work we focus on desktop solutions. We aim to provide a user-friendly environment for applying BEM in molecular electrostatics, using hardware and algorithmic acceleration. User-friendliness is provided by a Python interface to a GPU-enabled fast BEM (using PyCUDA). In this presentation, we will show benchmarking results of a BEM solver on GPU using an $O(N \log N)$ fast algorithm for the Yukawa kernel. The codes are being developed to be an open-source project.

We will show experimental results with physiologically relevant scales demonstrating that a full BEM calculation is indeed necessary. Even though the Yukawa kernel decays faster than, for example, the Laplace kernel, it does not decay fast enough to neglect far-field interactions (i.e., use a cutoff approach). Using a spherical molecule as a model, we find that in order to have an acceptable accuracy in the matrix-vector multiplication, at least half of the molecular surface needs to be considered in the matrix. Thus, a cutoff approach will still result in an $O(N^2)$ complexity, and neglecting the far field is not a feasible option when using large values of $N$.

In conclusion, the combination of fast algorithms and GPU architectures can enable a new level of computational research in biological applications, without the need to access large-scale systems and deal with complex code bases.

## Future-Proofing Fast Electrostatic Models for the Era of Massive Parallelism

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Matthew G. Knepley
(Computation Institute, University of Chicago, Chicago IL, USA)

Molecular simulations of proteins and nanosystems continue to grow rapidly in scale, making computation speed a critical challenge despite exponentially increasing computational power (via massively parallel supercomputers and the rise of graphics processing units, GPUs). Implicit-solvent models represent a valuable and widely used way to dramatically reduce calculation times, replacing tens of thousands of explicit solvent molecules (in biological fluids, water and dissolved ions) with much simpler models often based on continuum electrostatic theory, e.g. the Poisson or Poisson—Boltzmann partial differential equations (PDEs). Significant progress has been made to adapt PDE solvers to the incredibly demanding setting of molecular dynamics, but fast approximate models such as Generalized Born remain popular in many applications, due to their high accuracy and speed. Unfortunately, most of these fast models approximate Poisson and Poisson—Boltzmann models (which have well-known weaknesses) in a way that does not allow extensions to more advanced implicit-solvent theories, for instance involving nonlocal or nonlinear dielectric response. Therefore, to improve the accuracy and scalability of our simulations simultaneously, we must: (1) identify mathematical classes of models that can be computed using scalable algorithmic primitives, such as the fast multipole method; (2) develop approximation theories based on the underlying mathematical formalisms, e.g. variational interpretation of the Poisson equation; (3) extend these approximation theories to address more sophisticated physics, e.g. nonlocal dielectric theory or the fully nonlinear Poisson-Boltzmann equation. We have developed an approach called BIBEE (boundary-integral based electrostatics estimation) that meets all these challenges, providing a fast, mathematically rigorous, scalable, and future-proof electrostatic model for molecular physics

**David Basanta**
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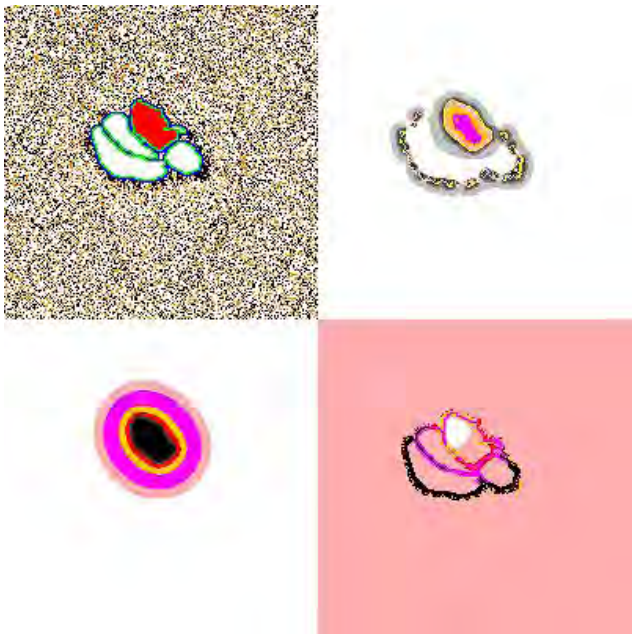
**Studying evolution in prostate cancer with agent based modeling**

Heterogeneity in prostate cancer is the driving force in somatic evolution which explains the emergence of resistance to therapies and relapse. We will show a computational agent based model of prostate cancer where tumour cells can adapt to the microenvironment and show how this evolutionary process is responsible and exploits the heterogeneity that makes prostate tumours so difficult to treat.



**Andrew M. Bate** and Frank M. Hilker, University of Bath, Department of Mathematical Sciences, Centre for Mathematical Biology, Bath BA2 7AY, UK.

## Rabbits killing birds: Hypopredation and limitations of hyperpredation

Biological invasions often damage island ecosystems. One such damaging consequence of biological invasions is hyperpredation. Hyperpredation is the increase in predation pressure from a generalist predator following the introduction of an alternative prey, typically a consequence of apparent competition between the two prey. Models for this have been devised that demonstrate this effect. However, hyperpredation may not always occur or may not always occur at the same strength.

In this talk, we will investigate how saturation in the predator's functional response effects the strength of hyperpredation. We will demonstrate that predator saturation can actually overturn hyperpredation into hypopredation, an increase in native prey, as a result of *apparent predation* between the two prey. This occurs when the alternative prey is 'poisoned prey', i.e. prey that have a handling time cost greater than the nutritional benefit for the predator. Consuming 'poisoned prey' can result in an increase or decrease in predator density. From this, we conclude that the invasion of established ecosystems by non-native prey can lead to more diverse consequences than previously thought.

# On the Influence of High-Order Nonlinear Fluctuations in the Multivariate SIR Master Equation

**Basil S. Bayati** and Philip A. Eckhoff
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(Dated: March 14, 2012)

We perform a high-order analytical expansion of the epidemiological susceptible-infected-recovered multivariate master equation, and include terms up to and beyond single-particle fluctuations. It is shown that higher-order approximations yield qualitatively different results compared with low-order approximations, which is incident to the influence of additional nonlinear fluctuations. The fluctuations can be related to a meaningful physical parameter, the basic reproductive number, which is shown to dictate the rate of divergence in absolute terms from the continuum equations more so than the total number of particles in the system. In epidemiological terms, the affect of single-particle fluctuations ought to be taken into account as the reproductive number approaches unity.

Keywords: Nonlinear Fluctuations, Master Equation, Susceptible-Infected-Recovered, Nonlinear Systems, Moment Equations, Perturbation Methods, Reproductive Number

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## Data-Driven Computational Modeling of Breast Tumor Aggressiveness

Normal mammary ducts are composed of two distinct layers of cells, luminal epithelial cells and basal myoepithelial cells, separated from the stroma by a surrounding continuous lining of the basement membrane attached to the myoepithelial outer layer. The homeostasis of the mammary duct, its structure and function are regulated by both the epithelial cells and the myoepithelial cells and their interaction. Myoepithelial cells for instance play a role in the regulation of the polarity of the luminal epithelial cells. Also, during lactation, the contraction of myoepithelial cells along the ducts facilitates milk ejection.

Recent studies suggest that interactions between myoepithelial cells and the neo-plastic epithelial cells play a significant role in the progression of pre-invasive breast cancers to invasive stage. While normal myoepithelial cells act as suppressors of uncontrolled cell growth, tumor myoepithelial cells promote invasion by degrading the basement membrane through production of matrix metalloproteinases.

Motivated by these observations, we developed a computational model of mammary ducts composed of individual myoepithelial and epithelial cells. By bridging this model with histopathological data we study the importance of the interactions between these two cellular layers in the initiation and progression of tumor invasion. We further investigate various biophysical properties of individual epithelial and myoepithelial cells and their relative role in the advancement of breast cancer from pre-invasive to invasive ductal carcinoma.

## Flu, where are you?

**Catherine Beauchemin**

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Abstract:

The modelling of the spread of an infectious disease within an individual or a cell culture has typically been done in a non-spatial manner: the population of cells in each state (susceptible, infected, dead, etc.) is tracked and evolved as a function of time alone using ODEs, with no regards for their spatial location. What do we miss when we assume spatial homogeneity? I will review models constructed with various levels of spatial representation for the spread of influenza within a host and/or cell culture. I will explore in which ways spatial distribution can affect the spread and severity of the infection, in particular with respect to cell tropism (preference of the virus for certain cell types) and the production of defective interfering particles.

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## A Mathematical Model to Simulate the Progression and Treatment of Brain Metastasis

The present work introduces a novel mathematical model that simulates the progression of brain metastasis as well as the effect of radiotherapy on cancerous and normal tissue. In clinical practice, an optimization of treatment outcome, which includes a maximization of tumor control while minimizing normal tissue toxicity, necessitates not only a quantification of the biological effect on cancerous but also on healthy tissue. Therefore, the present model extends the current mathematical approaches by also modeling the effect of radiotherapy on normal tissue. Ultimately, such models could allow for estimating the biological effect of different treatment schedules and, thus, could contribute to predictions of individualized therapy outcomes.

The progression of brain metastases is described on a macroscopic scale by means of a reaction-diffusion equation. This equation states that tumor cells either proliferate or migrate into surrounding healthy tissue. In addition to random motion cell migration due to adhesive forces is considered. At this, cells will be affected by the forces generated through adhesive binding with other cells. The effects of radiation are described by an extension of the linear-quadratic model. This extension offers in addition to low-dose hypersensitivity a high flexibility for integrating cell repair and varying therapy parameters (e.g. irradiation duration, treatment delays).
The increased intracranial pressure – a consequence of tumor progression – results in a compression and displacement of the surrounding tissue. To account for this expansive nature of the tumor, the tumor cell density is linked to a parametric deformation model.

Simulation of metastatic progression was performed by using a brain atlas with an isotropic resolution of 1 mm. The mathematical model was applied to a patient with two brain metastases from small-cell lung cancer. The metastatic lesions calculated with the model were compared to the lesions measured on contrast-enhanced T1 weighted images at three different time points prior to radiosurgery as well as one time point after radiosurgery. The results show that the progression of both brain metastases can plausibly be recovered in space and time.
The model was also used to quantitatively study the efficacy of irradiation under a variety of treatment schedules and dose distributions. The numerical results illustrate the potential of the proposed model in finding a trade-off between tumor control and normal tissue toxicity.

A novel mathematical approach is presented that allows for simulating the progression of brain metastasis and the effects of irradiation. Typically, radiation-induced cell death is modeled by the linear-quadratic model, which has shown to be limited in describing, for instance, incomplete-repair and high-dose radiation. To overcome these limitations, we introduced an extension to the standard approach that not only allows for incorporating prior knowledge about low-dose-hypersensitivity but also offers a high flexibility for varying therapy parameters. At this, we are able to analyze growth delays under different fractionations and dose distributions. First results for a patient diagnosed with brain metastasis suggest that this model can reproduce the visible part of the lesion as observed on contrast-enhanced T1 weighted images. Incorporation into clinical planning systems could ultimately help radiation oncologists to select the appropriate safety margin for radiosurgery of brain metastasis. Avenues for research in near future include a further validation in a larger series of patients as well as an extension to other types of external beam radiation therapies.

**James D. Benson**, Department of Mathematical Sciences, Northern Illinois University, DeKalb, IL, USA

## Optimal control of a class of PDE and state constrained bio-mass transport problems

There is a critical need for optimal protocols for the equilibration of chemical additives necessary for the cryopreservation of cells and tissues. Cells must be equilibrated with high concentrations of permeating chemicals (CPAs) before the cooling process, and this must be reversed after warming. This problem is well suited for mathematical optimization because the concomitant osmotically induced volume fluxes contribute to potential sources of cell damage that define state constraints, there is a time-dependent toxicity to these high concentrations that defines a cost functional, and the transport of water and solutes across cell membranes is well described by a nonlinear system of ordinary differential equations. If we view extracellular concentrations of these additives as controls, these pieces of the problem can be combined to formulate a state constrained optimal control problem. We have previously defined analytical time optimal controls for a two-solute system that governs transport across single-cell membranes that has driven exciting new applications in the field of cryopreservation. Here we develop new theory to extend the optimization to an arbitrary number of solutes. Next, we note that these optimal controls cannot, in application, be achieved at the cell membrane. In light of this, we present a theory of how to extend optimal controls away from the cell membrane by using inverse-problem techniques to solve the associated PDE constrained nonlinear optimal control problem with state constraints. Finally, we provide several real-world examples.

**Michael Berglund**, University of Georgia, Athens, GA, USA

Jason Cantarella, University of Georgia, Athens, GA, USA

## Computational Method for Identifying Space Polygons

As computer modeling often suffers from small errors, it can often be difficult to tell when computed polygons are one and the same. That problem becomes even harder as they are allowed to rotate in three-space. The focus of this poster is to describe and give examples of one method for overcoming these issues.

By utilizing the fact that the space of closed $n$-edge space polygons of fixed length 2 can be described as a projection from the space of orthogonal pairs of complex unit vectors in $n$-space, and embedding this construction in a natural projection from a sphere in quaternionic $n$-space, we are able to give it a metric arising from that of the Stiefel manifold $V_2(\mathbf{C}^n)$. Additionally, we can track polygons along the projected geodesics, to provide a visualization of a path one polygon must take to reach another. Moreover, all computations involved can be done quickly and efficiently, and allow for easy direct sampling of $n$-edged polygons according to this metric in $O(n)$ time.

# **RSV and HPIV:** do they interact?

**Samit Bhattacharyya** and Frederick R. Adler
*Department of Mathematics and Biology, University of Utah, Salt Lake City, UT, USA*

Pathogen- pathogen interaction, a form of epidemiological synergism, is an emerging arena of new research and understanding in studies of infectious disease in the health and clinical care. Pathogen interactions can be operational at different scales and is very common when they share a common host population. We focus on two closely related viruses in the Paramyxovirus family (data obtained from Department of Pediatrics and Biomedical Informatics, University of Utah):

- **Respiratory Syncticial Virus (RSV),** a cause of severe illness in very young children,
- **Human Parainfluenza (HPIV),** the current cause of the majority of cases of croup in the United States, which breaks into four distinct serotypes.

Though preliminary statistical analysis of correlation and regression on datasets indicates apparent interaction between them, but it does not exhibit the nature of interaction. To address the issue, we came up with two different hypotheses of interactions: cross-immunity and convalescence, and build up two different seasonally forced two-disease models. Using a variety of model-fitting approaches including trajectory-matching, probe-matching, and Bayesian methods, we estimate the strength of interactions along with other parameters such as amplitude of seasonality and rate of waning immunity.

**Lydia M. Bilinsky**, SoMSS, Arizona State University, Tempe, AZ, USA
Steven M. Baer, SoMSS, Arizona State University, Tempe, AZ, USA

## Slow passage through a Hopf bifurcation in spatially extended excitable systems: Some examples from neuroscience

Hopf bifurcation is a common mechanism by which a dynamical system featuring a constant parameter $p$ has a critical value $p_H$, referred to as the Hopf point, such that for values of $p < p_H$ the system approaches a steady state, while for values of $p > p_H$ the system enters into sustained oscillations. It is known that when $p$ is not constant in time, but rather is ramped up at a very slow rate from some initial $p_0 < p_H$, there is a delay in the onset of sustained oscillations: they do not ensue as soon as $p$ exceeds $p_H$. The parameter value $p_{crit}$ at which sustained oscillations do ensue for a given ramp depends on both the initial value of the ramp $p_0$ as well as its functional form. Several authors [2-3] have studied the case of a linear parameter ramp $p = p_0 + \epsilon t$, $\epsilon << 1$; Baer and Gaekel [1] have considered more general monotonic ramps, including accelerating ramps such as $p = p_0 + (\epsilon t)^2$ and deaccelerating ramps such as $p = p_0 + \sqrt{\epsilon t}$. The problem of slow passage through a Hopf bifurcation is ultimately a singular perturbation problem with tiny parameter $\epsilon$, the ramp speed. Baer and Gaekel showed that for a given parameter ramp, $p_{crit}$ can be obtained from the WKB method familiar in physics.

Such work dealt with models that have no spatial structure, for example, the Fitzhugh-Nagumo model of an excitable cell. This model features a parameter $I$, meant to represent injected current; the system has a Hopf bifurcation with respect to $I$, and Baer and Gaekel investigated its response to a slow current ramp $I = I_0 + f(\epsilon t)$. In the present work, we focus on two spatially extended systems from neuroscience. The first is a reaction-diffusion model of a passive cable studded with active spines obeying Fitzhugh-Nagumo dynamics. By passive cable we mean that the cable itself is not excitable, but provides a medium through which the spines, which are excitable, communicate. This system models a passive dendrite covered in dendritic spines. The second system is a reaction-diffusion model of an active Fitzhugh-Nagumo cable. By active cable we mean that the cable itself is excitable; this models a neuron's axon, which has embedded in its membrane ion channels which enable it to generate action potentials. For both of these systems, we apply boundary conditions which describe a situation in which a slow current ramp $I = I_0 + f(\epsilon t)$ is injected into one end of the cable, while the other end is sealed to current. Both linear and nonlinear current ramps were investigated.

It is found that the WKB method provides not only the value $I_{crit}$ which a slow current ramp must attain for sustained firing of action potentials to commence, but also the location along the cable at which this instability first shows itself. Furthermore, as $I_{crit}$ varies, so does this location, in a regular way. Hence, by manipulating the current ramp, we can choose $I_{crit}$, and with it the location along the cable where the approach to sustained oscillations is first apparent. In addition, we explain why the location at which instability first shows itself varies with $I_{crit}$ as it does. We do this by recognizing that the active cable is actually a limiting case of the spiny passive cable, in which we let the stem resistances approach zero while increasing the number of spines. Dendritic spines have bulbous heads and cylindrical stems connecting them to the dendrite; the degree to which they are electrically coupled to the dendrite is determined by their stem resistances.

All WKB predictions of $I_{crit}$ and the location at which instability first shows itself were tested against finite difference solutions of the system. Roundoff error is a serious issue when solving systems with slow paramaeter ramps, and we address this.

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## On Crawling Human Epidermal Keratinocytes

We present some results on biometrics and simulation of migrating human epidermal keratinocytes. Outlines of both cell body and lamella are determined by stochastic active contours that are driven by brightness gradients in time-lapse micrographs. The corresponding cell trajectories exhibit characteristic correlation features in protrusion and directionality [3cd]. In order to reproduce these features in a whole-cell model, we employ the continuum theory of reactive interpenetrating flow [2] and generalize an earlier approach to approximate the cell periphery [1]. The flow dynamics of the cytoplasmic sol- and gel-phases is represented by quadratic finite elements on a two-dimensional ring-like domain with free boundary [3ab]. Mutual coupling of intracellular actin network and transmembrane focal adhesions gives rise to stochastic translocation forces, which induce piecewise persistent cell motion.

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**Erin Bodine**, Rhodes College, Memphis, TN, USA
**Carrie Diaz Eaton**, Unity College, Unity, ME, USA

## First-year Biomathematics: Considerations, possible frameworks, and resources

In developing a first year mathematics course for biological sciences majors, what are the essential skills that need to be addressed? What are the resources out there for instructors of these non-traditional classes? The first lesson is that not one size fits all. It is a process to match curriculum with student and college needs, and we present two possible emergent frameworks. We will also share the resources we have used and built to save you time and energy. Lastly, we reflect and introduce the elements of assessment, student motivation, and undergraduate research that will be discussed in later presentations.

**Sarah Bogen, Capital University, Columbus, OH and NIMBioS: National Institute for Mathematical and Biological Synthesis, Knoxville, TN, USA**

**Jessica Robins, University of Tennessee and NIMBioS, Knoxville, TN, USA**

**Annet Westhoek, University of Wisconsin, Madison, WI and NIMBioS, Knoxville, TN, USA**

Shigetoshi Eda, Department of Forestry, Wildlife and Fisheries, University of Tennessee and NIMBioS, Knoxville, TN, USA

Andrew Kanarek, NIMBioS, Knoxville, TN, USA

Suzanne Lenhart, Department of Mathematics, University of Tennessee and NIMBioS, Knoxville, TN, USA

## Agent-based mathematical model for Johne's disease epidemiology and economy

Johne's disease is one of the most economically important diseases in the dairy industry. We recently developed a discrete deterministic model for Johne's disease epidemiology. The model was used to evaluate cost-effectiveness of disease control measures based on an improved diagnostic test. In the 2012 REU program, we aim to build an agent-based model based on the existing model for better understanding of Johne's disease epidemiology and economy. Students will have a chance to visit a dairy farm to learn cattle management practice, interact with veterinarians, and learn how to build/evaluate an agent-based model with user-friendly software.

**This is an Undergraduate Poster

# On the solutions and conservation laws of the model for tumor growth in the brain

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## ABSTRACT

We study the problem of tumor growth and its monitoring ranging from the simple model for the radially symmetric to the more complex case being the radially non-symmetric one. In each case, we take killing rate of the cancer cells dependent on the concentration of the cells. Using the idea of Lie symmetry analysis, solve the model equation to find certain exact solutions. We also study certain conservation laws for the model.

## Stochastic Models for Competing Species with a Shared Pathogen

Linda J. S. Allen
**Vrushali A. Bokil**

Abstract: We study the dynamics of deterministic and stochastic models for n competing species with a shared pathogen. The deterministic model is a system of ordinary differential equations for n competing species in which a single shared pathogen is transmitted among the n species. There is no immunity from infection, individuals either die or recover and become immediately susceptible, an SIS disease model. Analytical results about pathogen persistence or extinction are summarized for the deterministic model for two and three species and new results about stability of the infection-free state and invasion by one species of a system of n-1 species are obtained. New stochastic models are derived in the form of continuous-time Markov chains and stochastic differential equations. Branching process theory is applied to the continuous-time Markov chain model to estimate probabilities for pathogen extinction or species invasion. Finally, numerical simulations are conducted to explore the effect of disease on two-species competition, to illustrate some of the analytical results and to highlight some of the differences in the stochastic and deterministic models.

**Rebecca Borchering**, University of Florida, Gainesville, FL, USA
Hao Liu, Arizona State University, Tempe, AZ, USA
Mara Steinhaus, Johns Hopkins University, Baltimore, MD, USA
Carl Gardner, Arizona State University, Tempe, AZ, USA
Yang Kuang, Arizona State University, Tempe, AZ, USA

## A Simple Spatiotemporal Rabies Model for Skunk and Bat Interaction in Northeast Texas

Our research aims to develop an accurate model for the spread of rabies in skunk and bat populations. Simulations of the model show changes in the distribution and number of infected individuals over time. The study is based on information about skunks and bats in Northeast Texas and utilizes map data which displays the distribution of confirmed rabies cases in Texas. An accurate rabies distribution model will aid authorities by providing information about the most effective way to distribute rabies vaccine pellets. In addition, the visual qualities of our model simulations provide an engaging way to convey information about a known public health hazard to people from a variety of backgrounds.

Most existing models ignore reservoir species or model them with patchy models by ordinary differential equations. However, evidence for the influence of bats on the spatial distribution and rabies dynamics of skunks is supported by Texas map data of confirmed rabies cases. There appears to be a two to three year period in which initial dispersal is followed by a resurgence of infected individuals. This pattern is indicative of the skunk's role as a reservoir species for rabies.

Generally, the rabies virus spreads as infected individuals pass on the infection by biting susceptible individuals. Since infected bats can transmit rabies to susceptible skunks, we incorporate interspecies rabies infection by using a coupled system of differential equations for our model. Hence, the rate of infection for susceptible skunks is affected by the number of infected bats. Partial differential equations are used to account for general and rabid population random movement. Spatial modeling of rabies is particularly important because increased movement (lack of regard for territorial boundaries) is one of the symptoms of rabies.

Initial simulations of our model were applied to a Gaussian distribution of infected individuals. The result was that the peak of the infection decreased as infected individuals spread out from the center. Smaller waves of infection were indicated by periodic small increases in infected individuals. Simulations without bat to skunk infection only projected the decay of infected populations. The partial differential equation system is solved in MATLAB using an adaptive Runge-Kutta 4/5 order solver. No-flux Neumann boundary conditions are implemented.

After the trial simulations, confirmed case data from a $(300\text{ km})^2$ region in northwest Texas was used to set the initial distribution of infected skunks and bats. Distributions of susceptible, exposed, and recovered individuals were initialized similarly. Most parameter values are obtained or computed from the literature. Simulations of our model with and without the additional infection contributed by bats are compared to the confirmed case data from Texas. The simulations which account for interspecies infection more accurately represent the distribution of infected skunks and bats in our region of study. Our model qualitatively describes the change in distribution of rabies infected bats and skunks over time.

**David Bortz,** University of Colorado, Boulder, CO USA

### Accurate Experimental Design and Model Selection Computations

In the mathematical modeling of infectious diseases, it is always a challenge to construct a good model and it is common to find multiple proposed models for the same pathogenic phenomena. Typically the models are systems of differential equations, which the authors then fit to experimental data to infer conclusions about the biological system. We consider a model selection methodology which includes models for deterministic individual dynamics and random population effects. These are combined in the stochastic complexity model selection criterion which balances goodness-of-fit with a measure of statistical sophistication. The inverse problem concerning the distinguishability of a class of models will be discussed. In particular, a previously unaddressed issue concerns the relationship between random sources and those arising from the numerical discretization. For example, when modeling *in vivo* HIV infection dynamics under therapy, log-normally distributed errors are frequently assumed in measuring the viral plasma counts. A crucial component to the computation of the model selection criteria in involves estimating the log-likelihood which changes dramatically depending upon the absolute tolerance of the ODE solver. Analytical and computational results in the context of the HIV example will be presented as well as preliminary development on a method for addressing this issue.

**Beth Bradley**, University of Louisville, Louisville, KY, USA
Lee Gibson, Indiana University Southeast, New Albany, IN, USA
Stacy Rumph, Indiana University Southeast, New Albany, IN, USA

## The Search for a Dengue Reservoir in the *Aedes* Mosquito Population

Dengue is among the most prevalent vector-borne viral diseases worldwide. Approximately 3.5 billion people live in endemic areas, with 100 million cases reported annually. Moreover, the geographical area included in these endemic areas is growing rapidly, due to the spread of the mosquito vectors *Aedes aegypti* and *Aedes albopictus*. Dengue epidemics appear periodically, occurring approximately every 2 to 5 years, depending on location and climate. In this work, we are particularly interested in the question of how the virus is sustained between epidemic outbreaks. Recent studies indicate that vertical transmission from adult female to her eggs, is not sufficient to sustain the virus in a given locale, considering the timescale between epidemics. One theory suggests a reservoir in another host mammal other than humans. However, there are no known non-human primates in which viremia has been found. We investigate an alternative theory, in which the virus potentially is sustained within the mosquito population alone, by means of vertical transmission combined with horizontal transmission via necrophagy (the consumption of dead infected larvae by susceptible larvae).

The potential for horizontal transmission and parameters associated therewith are currently under investigation by S. Remold's research group at the University of Louisville. In collaboration with this research group, we introduce a simple mathematical model, based on the SI model, for the larval stage of mosquito development that includes terms for necrophagy. Given appropriate values for the parameters in this system, we show that there is a non-zero steady state of infected larvae, which could provide a reservoir for the disease during the time between epidemic outbreaks of dengue.

**Nicholas F Britton**, University of Bath, Bath, UK

## Interspecific kleptoparasitism

Although interspecific kleptoparasitism is widespread, theoretical models have focussed on the intraspecific case. We develop a game-theoretic model of interspecific kleptoparasitism, and consider its adaptive dynamics.

**Cameron Browne**, University of Florida, Gainesville, FL, USA

## Modeling HIV Dynamics Under Periodic Combination Drug Therapy

Treatment of HIV infected patients with a combination of antiviral medications is often successful in controlling viral load, but finding optimal dosing regimens remains a challenge for researchers. Mathematical modeling can provide insights into potential treatment strategies. In this talk, I will discuss the dynamical consequences of incorporating combination drug therapy in a classical within-host HIV model. I will consider two types of antiviral drugs, Reverse-Transcriptase Inhibitors and Protease Inhibitors, both of which have time-periodic efficacy functions. Using perturbation techniques and Floquet theory, I argue that the timing between dosages of the two different drugs can critically affect the virus dynamics. I will illustrate the theoretical findings with numerical simulations of the model assuming current estimates of HIV parameters. Understanding optimal timing of drug application may aid in designing treatment strategies, and it also motivates interesting questions for future research.

**Alexander Bucksch**, School of Biology and School of Interactive Computing, Georgia Institute of Technology, USA
Stefan Fleck, Department Environmental Control, North-West German Forest Research Institute, Göttingen, Germany
Joshua S. Weitz, School of Biology and School of Physics, Georgia Institute of Technology, USA

## Canopy network reconstruction from point cloud data

Quantitative description of tree canopy architecture is important for creating and validating mathematical growth models of botanical trees (1-2), estimating the interactions with the environment (3) and to describe phenotypic traits of the tree canopy (4). In addition to traditional field measurements, emerging technologies like terrestrial laser scanning enable us to capture a 3-dimensional view of the canopy organization within minutes. However, there are many challenges to decipher the resulting point cloud data and to describe the underlying canopy structure. Network models have been proposed based on theoretical grounds, as suitable approximations to the hierarchical structure of tree branches in the canopy. Here we show that it is possible to: (i) reconstruct canopy networks from point cloud data; (ii) characterize the statistical properties of these canopy networks. Despite the fact that global network models are sensitive to small sampling errors in the capturing process of the canopy organization, we show that they are powerful to discriminate trees of the same species under significantly different growing conditions.

In this case study experiment we compare 6 apple trees (*Malus x domestica* Borkh. cv. 'Honeycrisp'). Three of these six trees are grown in a so-called Trellis system, while the other 3 trees are free standing. All six trees are measured with two methodologies. 1.) A manual field measurement of the six trees capturing branches up to 1mm in diameter and 2.) A terrestrial laser scanner sampling branches between 5-10mm in diameter.

A terrestrial laser scanner represents the sampled tree as a point cloud in 3D by measuring the round trip time of the laser beam between the scanner and the tree surface. A recently developed algorithm to derive a skeleton description from laser scanned trees, (5), allows us to represent the canopy architecture as a loop-free graph, which can be analyzed in terms of the topology formed by branch tips and branching points whose neighborhood relation is given by the surface. In simplified network models, the number and type of side branches (a topological metric) and the internode length (a topological metric) over the order numbers given by the branching hierarchy are considered as sufficient to describe a branching network. Both parameters can be derived directly from the field measurement and the skeleton graph derived from the point cloud. Practically we obtain the network description by assigning the Horton-Strahler order to the skeleton graph. A Horton-Strahler order assigns the order number 1 to the youngest branches and maximal order number to the trunk with respect to the branching hierarchy. In contrast to the commonly used Horton-Strahler ratios we compute the so-called Tokunaga ratios whose development is summarized in (6). Tokunaga ratios have the benefit to exploit the complete skeleton-graph. Here, "complete" means that side branches of order difference greater than 1 with respect to the branch where they originate from are not omitted in the describing side-branch-statistics. We discriminate both growing conditions, i.e. Trellis vs. free-standing, by analyzing the side-branch-statistics and the internode length.

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## Modelling plant-pollinator interactions with mixtures of linkage rules

It is common to represent a mutualistic network as a bipartite graph in which nodes represent plant and pollinator species and lines represent interactions between plant pollinator pair. Many pollination ecologists recognize that a pollinator species that has a colour preference may be expected to have higher visit frequencies for plants of that colour. In contrast, no visits may be expected between flowers with long tubal lengths and insects with shorter proboscises. Hence a model for plant-pollinator species interaction probabilities should take these linkage rules into account. A pollinator species that has a colour preference may be expected to have higher visit frequencies for plants of that colour. In contrast, no visits may be expected between flowers with long tubal lengths and insects with shorter proboscises. Hence a model for plant-pollinator interaction probabilities should take these linkage rules into account.

Unfortunately, ecologists do not always know how many, or even which, traits are the main contributors to observed interactions. The Latent Dirichlet Allocation (LDA) model from artificial intelligence has been typically used to model text in a document as a finite mixture of topics, where each topic has a different distribution over the words in a vocabulary. Define an interaction group as a cluster of plant and pollinator species such that the probability of an interaction between plants and pollinators within an interaction group is higher than that between plant and pollinators across interaction groups. Then, the LDA model can be thought to model a pollinator species as a finite mixture of (latent) interaction groups in which plant and pollinator pairs that share common linkage rules are placed in the same interaction group. Although LDA requires that the number of interaction groups be known, we propose using a penalized score, such as the Bayesian information criterion to learn how many interaction groups best describe the observed interactions for a given dataset.

We present results from a simulation study that investigates the accuracy of interaction group identification under different network properties such as network size, number of interaction groups, and level of nestedness. The effectiveness of LDA did not depend on network size or the number of actual interaction groups. However, the accuracy of LDA decreased as the amount of nestedness increased.

Finally, we demonstrate the LDA on a real network of plants and pollinators in the Alpine meadow region.

**Hannah Callender,** University of Portland, Portland, OR, USA

## Challenges and Opportunities For Assessment in First Semester Biocalculus

A growing number of colleges and universities have created biocalculus courses to better meet the quantitative needs of their biology and life science majors. One argument for the creation of such courses is that these students are not exposed to the need for mathematics in their field of study, as the majority of applications in traditional calculus are geared towards physics and engineering. However, little research has been conducted on the advantages and successes of such biocalculus courses. Here I will share my experiences and assessment results from a first semester biocalculus course at the University of Portland, where I have tracked both student performance and attitudinal changes towards mathematics over the course of the semester.

**Jason Cantarella**, University of Georgia, Athens, GA, USA.
Tetsuo Deguchi, Ochanomizu University, Tokyo, Japan.
Clay Shonkwiler, University of Georgia, Athens, GA, USA.

### A new model for ring polymers with some exact solutions.

A fundamental mathematical problem in the analysis of ring polymers is the efficient generation and analysis of large samples of random closed space polygons. These model polymer configurations in good solvent. The essential question is this: what probability measure should be used to sample polygon space? A number of answers have been proposed for this problem. For instance, if we restrict to the finite set of lattice polygons, there is a natural counting measure on closed lattice walks. Other authors have restricted attention to the space of equilateral closed polygons in space, or to a space of closed polygons where the edgelengths are sampled from a Gaussian distribution. In all these cases, it has not been possible to directly sample the space of closed polygons; existing algorithms use Markov chain methods to converge to a distribution on polygon space. There are no rigorous results on how fast these methods converge to their limiting distributions.

In this talk, we give a new description of polygon space which allows us to give new theoretical and computational results. Our measure is based on a map from the Stiefel manifold of orthonormal 2-frames in complex $n$-space to the space of closed $n$-edge space polygons which was constructed by Jean-Claude Hausmann and Allen Knutson in 1997. While Knutson and Hausmann were interested in this map primarily as a way to analyze the symplectic and algebraic geometry of polygon space, we use versions of their map to push forward natural and highly symmetric probability measures to four spaces of polygons: closed and open polygons of $n$ edges and fixed (total) length 2 in space and in the plane.

In the case of an closed equilateral $n$-edge polygon, our measure restricts to the expected one: it is the subspace measure of $n$-tuples of vectors in the round $S^2$ which sum to zero. The constructions restrict from space polygons to the corresponding spaces of planar polygons in a simple way and we will be able to give planar versions of all our theorems.

The most important practical property of these measures is that it is very easy to directly sample $n$-edge closed polygons in $O(n)$ time (the constant is small), allowing us to experiment with very large and high-quality ensembles of polygons. The most important theoretical property of this measure is that it is highly symmetric, allowing us to prove theorems which match our experiments. We will be able to define a transitive measure-preserving action of the full unitary group $U(n)$ on $n$-edge closed space polygons of length 2. Using these symmetries, we will be able to explicitly compute simple exact formulae for the expected values of squared chord lengths and radii of gyration for random open and closed polygons of fixed length, with corresponding formulae for equilateral polygons. We can then obtain explicit bounds on how fast the chord lengths of a closed polygon converge to those of an open polygon as the number of edges increases, providing rigorous justification for the intuition that a sufficiently long polygon "forgets" that it is closed.

**Dalton Chaffee**, Bearden High School, Knoxville, TN, USA
Hayes Griffin, Bearden High School, Knoxville, TN, USA

## The Evolution of Sexual Imprinting

Sexual imprinting occurs when individuals acquire mating preferences by observing the phenotypes of other individuals in the population. Offspring might imprint on their fathers (paternal imprinting), mothers (maternal imprinting), or on randomly selected members of the parental generation (oblique imprinting). Imprinting is common in nature, and it is expected to have implications for speciation and for the evolution of sexual selection. However, how imprinting itself evolves is poorly understood. Past imprinting studies have compared the different modes of imprinting across a range of imprinting strengths, but they have not found evolutionarily stable states (ESSs). Here, for the first time, we have determined and compared candidate ESSs for each mode of imprinting when females are the choosy sex across a variety of imprinting costs and for a range of sexually dependent marker trait viabilities. When a fixed cost is imposed upon imprinting, no imprinting evolves. Also, when imprinting is put under no cost or a biologically reasonable relative cost, paternal evolves to become absolute while maternal and oblique evolve to an intermediate ESS or fail to evolve at all. When ESSs of different modes of imprinting compete, paternal always prevails when present. However, when maternal and oblique compete across a range of viabilities, either can prevail as the ESS, depending on t he magnitude of cost and the character of the marker trait. We conjecture that instances of maternal and oblique imprinting observed in nature arise primarily in systems in which paternal imprinting is not possible, such as when fathers are not present during child rearing.

**Arnaud Chauviere**, University of New Mexico, Albuquerque, NM, USA
John Lowengrub, University of California, Irvine, CA, USA
Vittorio Cristini, University of New Mexico, Albuquerque, NM, USA
Michael Lewis, Baylor College of Medicine, Houston, TX, USA

## From normal mammary gland development to breast tumor growth: step-by-step development of a multiscale modeling approach

The normal homeostatic processes used for formation and maintenance of a given tissue can be altered to lead to progressive changes in cellular behavior and tissue architecture, which can ultimately lead to the formation of a tumor. In 1998, an elite group of breast biologists and breast tumor researchers stated: Our limited understanding of the biology and developmental genetics of the normal mammary gland is a barrier to progress. The importance of understanding the connection between normal development and tumor growth is obvious when one considers just the currently unanswered question: What cell types within the normal mammary gland are capable of being the cells of origin for human breast tumors?

In this talk, I will present a data-driven modeling approach for the normal development of mammary gland based on cell-lineage and cell transport in the constraint geometry of the terminal end bud (TEB). I will show how we plan to extend this approach to investigate 1) spatial organization of the various cell types within the TEB and along the duct and 2) carcinogenesis and the early stages of breast cancer development.

At later times of the development, modeling breast tumor growth requires the description of billons of cancer cells resulting from the early development of the disease. Thusly, I will present a theoretical multiscale framework inspired from physical sciences to bridge the gap between the descriptions of a few thousand cells in a normal end bud, and billions of cells involved in a growing macroscopic breast tumor that would result from dysregulation of the homeostatic processes within the mammary gland.

Electrostatics: Numerical algorithms and biological applications
Organizers: Yongcheng Zhou (Mathematics, Colorado State Univ., Fort Collins, CO, USA); Weihua Geng (Mathematics, Univ. of Alabama, Tuscaloosa, AL, USA)

**Fast Electrostatic Calculation in Molecular Simulation**

Xiaolin Cheng
Oak Ridge National Laboratory

Molecular dynamics is a well-established technique for simulating complex systems in physics, chemistry, biology and materials science. However, fundamental hurdles remain in order for molecular dynamics to reach either spatial or temporal scale of most realistic systems. The biggest challenge is the lack of efficient and scalable algorithms for treating long-range interactions, i.e. Coulomb interactions, which mostly relies on fast convolution methods. In this talk, I will discuss some recent progress and challenges toward fast convolution algorithms with their application to molecular dynamics on emerging heterogeneous platforms.

## Multiscale and multiphyiscs modeling and simulation of proton transport through membrane proteins

**Duan Chen**[1] and Guowei Wei[2]

[1] Mathematical Biosciences Institute, The Ohio State University
[2] Department of Mathematics, Michigan State University

Proton transport is one of the most important and interesting phenomena in living cells; it plays many crucial roles in biological processes such as cellular respiration, ATP synthase, and cancer cell development. Due to special properties of protons and membrane channels, traditional convection-diffusion models are not suitable to study proton flux; quantum dynamics is instead adopted. However, extremely expensive computational costs are required for a full quantum model. The present work proposes a multiscale/multiphysics quantum dynamic in continuum model for proton transport through membrane proteins, in order to balance physical accuracy and simulation efficiency. The current model is in form of total energy framework, from which governing equations are derived. Advanced mathematical tools are developed to handle the challenges in simulations and validity of the proposed model is verifed through comparison of the simulations and experimental data.

**Frederick Chen**, Wake Forest University, Winston-Salem, NC, USA
Amanda Griffith, Wake Forest University, Winston-Salem, NC, USA
Allin Cottrell, Wake Forest University, Winston-Salem, NC, USA
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## Behavioral Responses to Epidemics in an Online Experiment

We report the results of a study we conducted using a simple multiplayer online game that simulates the spread of an infectious disease through a population composed of the players. We use our virtual epidemics game to examine how people respond to epidemics. Specifically, we look at the effects of prevalence, infection history, cost of self-protection, as well as other factors on the players' decision to engage in protective behavior during an epidemic. Our results show that player behavior evolves over the course of the game and is sensitive to the prevalence of the disease. There is limited evidence that the cost of self-protection and infection history have an impact on the decision to invest in self-protection.

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Whitney England, Department of Microbiology, University of Illinois at Urbana-Champaign, Urbana, IL, USA
Mark J. Young, Thermal Biology Institute and Department of Plant Sciences and Plant Pathology, Montana State University, Bozeman, MT, USA
Rachel J. Whitaker, Department of Microbiology and Institute for Genomic Biology, University of Illinois at Urbana-Champaign, Urbana, IL, USA
Joshua S. Weitz, School of Biology and School of Physics, Georgia Institute of Technology, Atlanta, GA, USA

## Quantifying Strain Dynamics of CRISPR-Induced Host-Viral Coevolution: Sweeps and Coalitions

The dynamics of hosts and pathogens are driven by ecological interactions and evolutionary events. As the processes of ecology and evolution lead to complex behavior which are difficult to follow experimentally, ecoevolutionary models describing the dynamics of host-pathogen interactions are necessary to determine the essential factors driving growth and diversification of populations. The recent discovery of the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) system which acts as an immune defense in over 40% of bacteria and 90% of archaea (hosts) alters how evolution facilitates the interaction of hosts and viruses. The CRISPR immune system uses host-incorporated viral DNA to provide immunity against invading genetic material, such as viruses.

Recently, we introduced a multi-scale model of dynamic coevolution between hosts and viruses in an ecological context that incorporates CRISPR immunity principles [1]. In that work, we analyzed the model to test whether and how CRISPR immunity induces host and viral diversification and maintenance of coexisting strains. We showed that hosts and viruses coevolve to form highly diverse communities through punctuated replacement of extant strains. The populations have very low similarity over long time scales. However over short time scales, we observe evolutionary dynamics consistent with incomplete selective sweeps of novel strains, recurrence of previously rare strains, and sweeps of coalitions of dominant host strains with identical phenotypes but different genotypes.

Here, we analyze our previously developed multi-scale model of coevolution between hosts and viruses involving the CRISPR immune mechanism to explore the molecular drivers of strain dynamics. We show that diversity of strains develops and is maintained within the populations through a combination of overlapping ecological and evolutionary times-scales as well as phenotype similarities resulting from disparate genotypes. Furthermore this observed diversity is not a constant set of co-existing strains but rather involves an ever-changing set of strains. We present metrics to quantitatively distinguish dynamics when one strain (sweep) versus multiple strains (coalition) dominant the population and describe characteristic signatures of each of these population level signatures. The analysis of our model will help understand the implications of signatures found in metagenomic data of microbial communities where CRISPR systems are found.

[1] L. M. Childs, N. L. Held, M. J. Young, R. J. Whitaker and J. S. Weitz, (in press). Multi-scale Model of CRISPR-induced Co-evolutionary Dynamics: Diversification at the Interface of Lamarck and Darwin, Evolution.

**Rebecca H. Chisholm**, The University of Melbourne, Melbourne, VIC, Australia
Barry D. Hughes, Kerry A. Landman, The University of Melbourne, Melbourne, VIC, Australia

## Building a Morphogen Gradient without Diffusion in a Growing Tissue

In many developmental systems, spatial pattern arises from morphogen gradients, which provide positional information for cells to determine their fate. Typically, diffusion is thought to be the mechanism responsible for building a morphogen gradient. An alternative mechanism is presented here. Using mathematical modeling, we demonstrate how a non-diffusive morphogen concentration gradient can develop in axially growing tissue systems, where growth is due to cell proliferation only. Two distinct cases are considered: in the first, all cell proliferation occurs in a localized zone where active transcription of a morphogen-producing gene occurs, and in the second, cell proliferation is uniformly distributed throughout the tissue, occurring in both the active transcription zone and beyond. A cell containing morphogen mRNA produces the morphogen protein, hence any gradient in mRNA transcripts translates into a corresponding morphogen protein gradient. Proliferation-driven growth gives rise to both advection (the transport term) and dilution (a reaction term). These two key mechanisms determine the resultant mRNA transcript distribution. Using the full range of uniform initial conditions, we show that advection and dilution due to cell proliferation are, in general, sufficient for morphogen gradient formation for both types of axially growing systems. In particular, mRNA transcript degradation is not necessary for gradient formation; it is only necessary with localized proliferation for one special value of the initial concentration. Furthermore, the morphogen concentration decreases with distance away from the transcription zone, except in the case of localized proliferation with the initial concentration sufficiently large, when the concentration can either increase with distance from the transcription zone or sustain a local minimum. In both localized and uniformly distributed proliferation, in order for a concentration gradient to form across the whole domain, transcription must occur in a zone equal to the initial domain size; otherwise, it will only form across part of the tissue.

Ching-Shan Chou
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**Mathematical Modeling of Cell Morphological Change Induced by Pheromone Gradient in Yeast**

Cell morphogenesis is a fundamental process that underlies cell differentiation, behavior, and response to internal and external cues. Polarized morphogenesis has been established to require the rearrangement of the actin cytoskeleton, which is downstream of membrane signaling events and involved in protein, organelle and secretory vesicle transport toward the site of growth. Persistent cell polarization requires the initiation, establishment, and maintenance of the polarized site with different mechanisms being proposed to explain these steps. Based on existing evidence, cell polarization of the yeast S. cerevisiae during mating is likely maintained through the transport of vesicles to and from the membrane, therefore resulting in cell morphology being dependent on the balance between endocytosis and exocytosis. While our experiments show that the morphology of yeast mating projections is affected by changes in pheromone concentration, we propose that a further understanding of the underlying mechanisms can be elucidated through mathematical modeling of the system. To achieve this, we have expanded previously developed models of the yeast mating pathway to include a dynamically evolving cell membrane that is linked to the underlying molecular signaling species through endocytosis and exocytosis. Our simulation results are shown to be in good agreement with the experimental measurements, and our model thus provides a plausible explanation for the pheromone concentration dependent cell morphologies.

**Yao-li Chuang**, Department of Pathology, University of New Mexico, Albuquerque, NM, USA
Vittorio Cristini, Department of Pathology and Department of Biomedical Engineering, University of New Mexico, Albuquerque, NM, USA
Ying Chen, Department of Mathematics, University of California, Irvine, Irvine, CA, USA
Xiangrong Li, Department of Mathematics, University of California, Irvine, Irvine, CA, USA
Hermann B. Frieboes, Department of Bioengineering, University of Louisville, Louisville, KY, USA
John S. Lowengrub, Department of Mathematics, University of California, Irvine, Irvine, CA, USA

## Adapting a tumor growth model to an evolving domain using a diffuse-domain approach

Tumor growth at the macroscopic scale is often characterized by emerging spatiotemporal patterns, which are believed to be a contributing factor to subsequent tumor infiltration and metastasis. Furthermore, the nontrivial spatiotemporal structures can have profound effects on the collective response of tumor cells to their microenvironmental molecules, including chemotherapeutic drugs. Therefore, understanding the spatiotemporal evolution of tumor growth represents an essential step towards the prevention of tumor spread and the engineering of efficient drug delivery protocols.

Various partial differential equation (PDE) models have been formulated to study the spatiotemporal dependence of tumor progression at the macroscopic scale. Among the efforts, we derived a diffuse-interface model based on the Cahn-Hilliard equation and constructed an adaptive multigrid solver to efficiently compute its numerical solutions on a cartesian mesh [ *Wise et al., 2008, Three-dimensional multispecies nonlinear tumor growth - I Model and numerical method, J. Theor. Biol. 253, 524-543* ]. Like many other macroscopic tumor growth models, our model assumed a tumor developing in a mechanically non-restricting environment, where the host tissue is infinitely compliant to the tumor progression. However, most tumors are developing within the confinement of a specific organ, where the confining environment, albeit not completely compliant, can evolve in response to the mechanical pressure from the tumor growth. The proposed tumor growth model may only be applicable within this time-dependent domain.

Using a novel diffuse-domain method [ *Li et. al., 2009. Solving PDEs in complex geometries: A diffuse domain approach, Commun. Math. Sci. 7, 81-107* ], we adapt our tumor growth model to an evolving domain through the weak form of the PDEs. The domain can be solved as a free-boundary problem on a Cartesian mesh, while appropriate boundary conditions are imposed on the domain boundary. We apply this approach to model the growth of lymphoma in a lymph node. The capsule of the lymph node constrains the movement of the lymphoma cells and the lymph fluid, which in turn causes the lymph node to swell. An angiogenesis model is also adapted to describe the neovasculature induced by the lymphoma tumor.

**Maciej Chudek**, University of British Columbia, Canada
Joseph Henrich, University of British Columbia, Canada

## How exploitation launched human cooperation: A model of negative indirect reciprocity

The evolution of cooperative human communities remains a central scientific puzzle. Most models emphasize positive reciprocity or coordinated punishment. These models target the latter stages of the evolution of human sociality as they assume the existence of (1) well-defined social roles (e.g., donors or punishers) or institutions (e.g., punishment pools or signal meaning), (2) sophisticated cognitive abilities for recognizing and responding to these socially defined roles and expectations, and (3) harmonious communities, where the benefits of mutual aid are not undermined by mutual exploitation.

Here we lay a foundation for these latter stages by describing how Negative Indirect Reciprocity (NIR) can suppress exploitation (e.g., stealing, rape, etc.) to (1) create harmonious communities, and (2) sustain supporting public goods contributions, while at the same time producing conditions that favour a sensitivity to shared social expectations, and the ability to recognize violations of these expectations. This negative context, where 'cooperating' means 'not exploiting someone', poses a distinct challenge since such cooperative acts are unobservable. While existing models depend on efficient helping (high benefits at low cost), NIR models stabilise harmonious communities when exploitation is inefficient (victims are seriously hurt by exploiters who benefit little, a large net loss). These inefficient circumstances are potentially more plausible earlier in human evolutionary history.

Our approach recasts the emergence of cooperative communities by showing how NIR can suppress opportunistic exploitation (e.g., of the weak, sick or injured) and then selectively revoking this safety net to enforce costly adherence to community-wide cooperative expectations. These models provide novel insights and suggest new challenges to the evolution of our species' distinct form of sociality.

**Stanca, Ciupe, Virginia Tech, Blacksburg, VA, USA**

Sarah Hews; Hampshire College, Amherst, MA, USA

## The role of e-antigen in immunological tolerance and activation during HBV infection

The presence of circulating hepatitis B e-antigen may promote hepatitis B chronic infection by serving as an immunotolerance agent capable of inducing T-cell clonal deletion, ignorance and anergy. Sudden loss of e-antigen leads to the restoration of T-cell effector function and consequently to liver cell death. Using mathematical models, we investigate the host-virus interactions, determine the factors that lead to viral persistence when e-antigen is present and study the changes in these dynamics when e-antigen is lost as a result of e-antigen seroconversion or virus mutation. Using the seroconversion model, we show that high antibody levels, which completely remove e-antigen, successfully restore effector function to anergic T-cells while reducing the overall liver cell death. Using the mutation model, we show that intermediate mutation rates are associated with high levels of liver cell death, while complete loss of the wild virus is associated with mild liver disease and emergence of low mutant virus levels. The results are compared with virus concentrations and immune activation markers from patients with prenatal HBV infections.

**James Clarke**, Centre for Mathematical Biology, University of Bath, Bath, UK
Jane White, Centre for Mathematical Biology, University of Bath, Bath, UK
Katy Turner, School of Social and Community Medicine, University of Bristol, Bristol, UK

## Modelling the short-term dynamic impact and implications of control strategies for *Chlamydia trachomatis*

Chlamydia has a significant impact on public health provision in the developed world. Using simpler models (including pairwise approximation equations) we investigate how much effect control programmes could have over short time-scales relevant to policy makers. At this scale dynamic effects are important to take into account, and the responsiveness of each model is just as important as steady state predictions. We use output from the models to estimate critical measures namely prevalence, incidence and positivity in those screened and their partners. We combine these measures with costing data and tools to estimate the economic impact of different intervention strategies. This dynamic approach highlights the importance of model selection when performing cost-effectiveness analysis, and shows that simpler models can be useful in conjunction with more complex stochastic simulations. However, too simple a model can result in dramatically different predictions.

**Christina Cobbold**, School of Mathematics and Statistics, University of Glasgow, UK
Frithjof Lutscher, Department of Mathematics and Statistics, University of Ottawa, Canada

## From diffusion models to patch models using mean occupancy time.

Patch models, coupled systems of ODEs, have been widely used by ecologists to study population dynamics on heterogeneous landscapes. The landscape is viewed as a system of coupled homogeneous patches with migration between these patches. This simplification typically looses any explicit connection between migration and individual level movement rules on the landscape, but has the advantage that it is relatively simple to analyse. In contrast, diffusion models can include explicit mechanistic movement rules for a population, but have the disadvantage of being difficult study on complex landscapes. Our approach is to study questions of population persistence on heterogeneous landscapes by deriving an ODE patch model approximation of a corresponding diffusion model which retains information about the underlying movement rules. To do this we introduce the idea of mean occupancy time (MOT), the time an individual spends in a given region. We use MOT to approximate the eigenvalues of the diffusion models which in turn allows us to obtain migration rates for our patch model. We demonstrate that the MOT patch model accurately approximates the persistence conditions of the underlying PDE models in a range of examples. Moreover the approach can also be used to estimate the spatial distribution of a population at equilibrium.

**Sarah Collier, University of Dayton, Dayton, OH and NIMBioS: National Institute for Mathematical and Biological Synthesis, Knoxville, TN, USA**

**Faryal Khan, North Carolina State University, Raleigh, NC and NIMBioS, Knoxville, TN, USA**

**Olatomiwa Lasebikan, Fisk University, Nashville, TN and NIMBioS, Knoxville, TN, USA**

Heather Finotti, Department of Mathematics, University of Tennessee and NIMBioS, Knoxville, TN, USA

R. Tucker Gilman, NIMBioS, Knoxville, TN, USA

## Modeling the evolution of sexual imprinting

Sexual imprinting is a process by which an individual's mate preference is learned through interaction with the environment. Young individuals that imprint on parents, siblings, or neighbors will look for similar traits in potential mates. Learned mate preferences are believed to play an important role in speciation, but how imprinting strategies evolve is only partly understood. We will use novel mathematical models to ask how imprinting strategies evolve, and how evolved strategies are likely to differ between males and females.

**This is an Undergraduate Poster

**Shannon Collinson**, Department of Mathematics and Statistics, York University, Toronto, ON, Canada
Dr. Jane Heffernan, Department of Mathematics and Statistics, York University, Toronto, ON, Canada

## The effects of media on influenza infection: An agent based Monte Carlo simulation

Media reports affect social behaviour during epidemics and pandemics. Changes in social behaviour, in turn, affect key epidemic measurements such as peak magnitude, time to peak, and the beginning and end of an epidemic. The extent of this effect has not been realized. We have developed mathematical models of influenza spread based on a Susceptible-Exposed-Infected-Recovered (SEIR) model including the effects of mass media. Different functions representing media are studied within the context of the models in order to evaluate the effect of media on key epidemic measurements. We have also developed an agent based Monte Carlo (ABMC) simulation to determine the variability in these key epidemic measurements, so as to provide some insight in to the effects of mass media on epidemic data.

**From Biocalculus to Undergraduate Research. Timothy D. Comar,** Benedictine University, 5700 College RD, Lisle, IL 60532, tcomar@ben.edu

One of the goals of the biocalculus courses at Benedictine University is to prepare students to engage in research in mathematical biology, mathematics, or related areas upon completion of the course. This presentation will focus on course activities that help prepare students to begin research work and will highlight subsequent undergraduate research projects completed by former biocalculus students. Projects topics include models in integrated pest management, the spread of a nonindigenous, invasive, and gene regulatory networks.

**Bifurcations in Differential Equations Models for Gene Regulatory Networks. Timothy D. Comar,** Benedictine University, 5700 College RD, Lisle, IL 60532, tcomar@ben.edu

We investigate differential equations models for gene regulatory networks with three or four genes. We establish conditions for which these models exhibit stable oscillations. These conditions depend on parameters representing time scales and the cooperativity of the regulating interactions. As these models can exhibit either oscillatory behavior or stable behavior, bifurcations occur between the regions in parameter space in which oscillatory and stable behavior manifest. We describe these bifurcations, which include Hopf. bifurcations.

**Jessica M. Conway**, Department of Mathematics, University of British Columbia, Vancouver, BC, Canada
Bernhard Konrad, Department of Mathematics, University of British Columbia, Vancouver, BC, Canada
Daniel Coombs, Department of Mathematics, University of British Columbia, Vancouver, BC, Canada

## Stochastic model of HIV prevention using anti-retroviral drugs

Drug treatments for HIV very effectively control chronic infection. They can also be used to prevent the initiation of HIV infection, either in advance of risky exposure (termed pre-exposure prophylaxis, PrEP), or very shortly after accidental exposure to the virus (termed post-exposure prophylaxis, PEP). To investigate this use of HIV treatments, we developed a multi-type, continuous-time branching process model of the very early stages of HIV infection within-host. We extract extinction probabilities for HIV from equations for the probability generating function, derived from the related Chapman-Kolmogorov equation. We will discuss model predictions regarding the effectiveness of PrEP/PEP depending on factors such as drug type, post-exposure initiation time, and duration of treatment.

**Michael H. Cortez**, Georgia Institute of Technology, Atlanta, GA, USA
Joshua S. Weitz, Georgia Institute of Technology, Atlanta, GA, USA
Stephen P. Ellner, Cornell University, Ithaca, NY, USA

## Comparing the Eco-Coevolutionary Dynamics and the Eco-Evolutionary Dynamics of Predator-Prey Systems Using Fast-Slow Dynamical Systems Theory

Ecologically important traits can evolve at the same rate as changes in species' ecological dynamics (e.g. population densities or spatial distributions). This interaction between ecological and evolutionary processes with comparable time scales can potentially alter the ecological dynamics of the system or lead to coevolutionary dynamics that would be unexpected based on the evolutionary dynamics of a single species. In this talk, we will focus on the consequences of the interactions between ecological and evolutionary processes in predator-prey systems. In particular, we focus on the question 'how do coevolutionary dynamics differ from evolutionary dynamics with a single evolving species in their effects on the populations dynamics of predator-prey systems?'

To address this question we consider a general predator-prey model where the two species are evolving nearly instantaneously. Our model is an extension the model in Cortez and Ellner (2010) where a single species evolves. While evolutionary processes are not nearly instantaneous in natural systems, there are two main advantages of considering the fast evolution limit. First, via fast-slow dynamical systems (or Fenichel) theory, the dimension of the system can be reduced from four to two. This facilitates the analytical analysis of the system and allows one to derive biological and mathematical conditions that characterize when and what kinds of effects evolutionary processes have on the ecological dynamics of the system. Second, the results and conclusions derived in the fast evolutionary limit yield insight into the effects coevolutionary dynamics have on the ecological dynamics of the system when evolution is not as fast.

Based on comparisons between the current model and the model in Cortez and Ellner (2010), our analysis yields biological and mathematical conditions under which the eco-coevolutionary dynamics of the systems can be accurately predicted by the subsystems that have a single evolving species. However, we also find conditions under which the single evolving species subsystems do not accurately predict the eco-coevolutionary dynamics. In these cases, the interaction between the evolutionary dynamics of the two species yield unexpected coevolutionary dynamics, e.g. one species can become trapped at a fitness minimum or the fitness maximum of both species can become evolutionarily unstable. Some of these dynamics have been observed previously in the literature (e.g. Abrams and Matsuda 1997) and our analysis reveals the general biological and mathematical mechanisms driving those phenomena. This analysis suggests how some of these different cases can be identified from experimental data and what (sometimes unexpected) effects rapid coevolutionary dynamics can have on ecological dynamics.

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## A Comparative Theoretical Study of Age-structured Fish Subpopulations

Author: Elizabeth Councill, University of Miami – Marine Biology and Fisheries and Department of Mathematics

Many species of harvested fish undergo changes in reproductive strategies and behaviors as a consequence of fishing pressure or changes in habitat. Many of these changes occur in subpopulations where management efforts are disproportional across large spatial scales or where the habitat of the population in a particular area is altered. This project provides a new way of modeling such populations where subpopulations are reproductively isolated and shows how using a comparative modeling approach, we can understand the processes that dictate the age structure of these populations. The model derived in this study is a discrete-time Leslie process, the components of which are functional response curves derived from modeled behaviors. Here, I present a brief overview of the derivation of the model with underlying assumptions, solvability, and a brief analysis of the solution. I also present a simplified two-stage model of a fish population in which both mature and immature individuals are present with a comparison between individuals who are reproducing in multiple spawning seasons and those who spawn in a single large burst. Finally, I present an outline of the ongoing research being done on this project as it applies to harvested marine fishes, particularly Atlantic Tarpon, Bluefin Tuna, Swordfish, and Skipjack tuna.

**Elena Crosley, Bowdoin College, Brunswick, ME and NIMBioS: National Institute for Mathematical and Biological Synthesis, Knoxville, TN, USA**

**Arielle Nivens, Maryville College, Maryville and NIMBioS, Knoxville, TN, USA**

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Cristina Lanzas, Department of Comparative Medicine, Veterinary College, University of Tennessee and NIMBioS, Knoxville, TN, USA

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## Modeling *Salmonella* transmission in swine

Salmonellosis is one of the most common bacterial food-borne illnesses. Farm animals, including cattle, pigs, and chickens are reservoirs for *Salmonella*. In recent years, the proportion of *Salmonella* resistant to several antimicrobial drugs (multi-drug resistant strains) has increased. Humans infected with multidrug resistant strains are at greater risk of hospitalization and death compared to patients infected with susceptible strains. Prevention of human salmonellosis depends on decreasing the prevalence of infections in farm animal hosts as well as identifying and intervening along key transmission routes. This REU project will focus on developing mathematical models of *Salmonella* transmission in swine farms to better understand the factors that favor the transmission and the persistence of these multidrug resistant *Salmonella* in different farm environments.

**This is an Undergraduate Poster

Title:
Mechanical modeling of bacterial cell division and the FtsZ ring

Authors:
Eric Cytrynbaum

Abstract:
FtsZ, a cytoskeletal protein homologous to tubulin, is the principle constituent of the division ring in bacterial cells. It is known to have force-generating capacity in vitro and has been conjectured to be the source of the constriction force in vivo. Several models have been proposed to explain the generation of force by the Z ring. In this talk, I will discuss a modeling approach to understanding the mechanics of the division ring in bacterial cell division through which we test out a long-standing hypothetical mechanism and use it to estimate the mechanical properties of the FtsZ ring.

**Donghai Dai,** Cory Howk, Brandon Beck, Dept. of Obstetrics and Gynecology, University of Iowa, Iowa City, Iowa, USA

## The origin and mathematical characterization of cancer stem cells based on computer simulated tumor development in uterine epithelium

We have developed a mathematical model of human endometrial cancer previously (Dai et al PLoS 2011, v6:e16859). The information of peak epithelial tissue size, and the time of proliferation for a single stem cell to form a clone in human uterine epithelium, provides the basis for simulating the normal tissue regeneration process and has allowed us to develop some preliminary criteria, such as the number of stem cells committed every day and the normal life cycle of a committed epithelial cell before senescence. Based upon the mathematical description of the process of normal tissue regeneration involving billions of cells in the uterine epithelium, we have simulated the cancer incidence as a result of quantitative interactions of genetic alterations and environmental factors occurring in the human uterine epithelium, leading to a result consistent with the epidemiological data. The tumors created by computer simulations have allowed us to analyze their entire development process and the etiological dynamics associated with that process in order to understand the origin of a model tumor and its intra-tumor heterogeneity.

Based upon the commonly accepted concept that a malignant tumor is monoclonal in origin and upon analysis of the phylogenetic lineage of individual cells in each of approximately 80 simulated tumors, we developed a simple mathematical characterization of a cancer cell in relation to the parameters established for the description of normal cell development. We found that the cancer ancestor cells (the first cancer cell that eventually forms the entire tumor) have varying degrees of loss of differentiation and, consequently, growth potential. The first cancer cell is typically formed after 17 divisions of effectively normal cells and has a differentiation score of 0.3 versus a score of 4.0 for a terminally differentiated cell. Thus, the cancer ancestor cell under this characterization is very similar in differentiation status to cancer stem cells, completely undifferentiated cells.

Among all simulated tumors we analyzed, all cancer stem cells are created through the de-differentiation process from well-differentiated cells as well as the result of further de-differentiation of cancer cells. The probability of a cancer stem cell resulting from direct transformation from a tissue stem cell is very low, since our simulation has not detected any case of direct transformation among the 80 simulated tumors.

We have found that the conversion between cancer stem cells and cancer cells through differentiation and de-differentiation under hormone influence is dynamic with a varying rate, resulting in dramatically different sizes of cancer stem cell pool in individual tumors. While the difference in cellular differentiation between a typical cancer cell and cancer stem cell is very small, there is a significant difference in their potentials to create a mass themselves, and the most significant difference lies in their capability to establish metastatic lesions in ectopic sites. A cancer stem cell after surviving the metastatic process will have a significantly higher probability to form metastatic lesions.

The modeling of solid tumor formation in normal uterine epithelium has provided some insights into the role of cancer stem cells in the oncogenic process and tumor progression.

**Abhiram Das,** School of Biology, Georgia Institute of Technology, Atlanta, GA, USA
Charles A. Price, School of Plant Biology, University of Western Australia, Australia
Alexander Bucksch, School of Biology and School of Interactive Computing, Georgia Institute of Technology, Atlanta, GA, USA
Joshua S. Weitz, School of Biology and School of Physics, Georgia Institute of Technology, Atlanta, GA, USA

## SoLID – An Online Community Database of Leaf Images

Plant leaves exhibit different classifying features such as vein network structures, colors, and chemical concentrations. Analyzing and quantifying such features enables the functional interpretation of leaves. Leaf images are often maintained in curated collections. These collections are not always easily accessible to researchers. However, there is a significant value in the digital analysis of collections, if made available to the larger scientific community. Here, we introduce a novel mechanism to do so via a Social Leaf Image Database (SoLID). SoLID is an online database with a social network mechanism for a community of researchers to contribute, access and share leaf images that also leverages resources of curated collections.

In recent years there has been growing interest in leaf images for a number of reasons. These include: (1) Interest in allometric scaling relationships between foliage structure, chemistry and physiological characteristics. Characteristic correlations between leaf size and climate have been employed to gain insight into adaptive modifications in leaf size (Niinemets et al., 2007). (2) Foliar color is of great interest to resource managers and scientists as a visual indicator of plant health. Digital color analysis is a popular and cost-effective method to evaluate foliar nutrition and health in response to environmental stresses (Murakami et al., 2005). (3) Significance of leaf venation network structure in many areas of plant biology including impact of leaf vein geometry and network on hydraulic conductance. Segmentation and analysis of structure of leaf vein network and areoles (Price et al., 2011). Image processing is a popular and cost-effective method to evaluate leaf color and extract venation networks and areoles, from which we can establish allometric relationships.

SoLID enables researchers around the world to store, annotate, search and share their leaf image collections through a single web interface. The unique features of SoLID can be categorized into two groups: community features and technological features. The community features allow a user to 1) mark an image collection as private or public, 2) share image collections with a trusted user community, 3) post comments on images and its meta-data, 4) flag images for review, etc. The community feature also enables non-scientists with important data to contribute to scientific research, through a trusted user mechanism. From a technology point of view, we have developed a database back-end specifically targeted for leaf images. SoLID allows plant biologists and trusted users to store leaf images online with their meta-data, create collections of images, upload and download images from the collections. An open programming interface allows external image processing software to access marked images from the SoLID. The power of the system comes from different user access privileges on the resources, accessing the database from any image processing platform and one destination for all types for leaf images. Images in the database are linked to other online image databases such as USDA plant database, CalPhotos, Morphbank, Encyclopedia of Life and Google images. We demonstrate the programming interface by using the open source software Leaf GUI (Price et al. 2011, www.leafgui.org) to connect to SoLID, download images, extract leaf venation patterns from images and analyze them.

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**Fordyce Davidson**, University of Dundee, Scotland, UK
Nicola Stanley-Wall, University of Dundee, Scotland, UK

## Selective Heterogeneity in Exoprotease Production by *Bacillus subtilis.*

Bacteria have elaborate signalling mechanisms to ensure a behavioural response that is most likely to enhance survival in a changing environment. It is becoming increasingly apparent that as part of this response, bacteria are capable of cell differentiation and can generate multiple, mutually exclusive co-existing cell states. These cell states are often associated with multicellular processes that bring benefit to the community as a whole but which may be, paradoxically, disadvantageous to an individual subpopulation. How this process of cell differentiation is controlled is intriguing and remains a largely open question. In this talk, we consider an important aspect of cell differentiation that is known to occur in the Gram-positive bacterium *Bacillus subtilis*: we investigate the role of two master regulators DegU and Spo0A in the control of extra-cellular protease (EPS) production. EPS is required to adhere the cells together and in mutant $EPS^-$ strains, the biofilm visibly lacks structural integrity. Recent work in this area focussed the on role of DegU in this process and suggested that transient effects in protein production were the drivers of cell-response heterogeneity. Here, we provide a complementary analysis of this regulatory system that investigates the roles of both DegU and Spo0A in extra-cellular protease production. In doing so, we present a mechanism for bimodality, or system heterogeneity, without the need for a bistable switch in the underlying regulatory network. Moreover, our analysis leads us to conclude that this heterogeneity is in fact a persistent, stable feature. Our results suggest that system response is divided into three zones: low and high signal levels induce a unimodal or undifferentiated response from the cell population with all cells OFF and ON, respectively for exoprotease production. However, for intermediate levels of signal, a heterogeneous response is predicted with a spread of activity levels, representing typical "bet-hedging" behaviour.

## Spatial localization of Par proteins in the early *C. elegans* embryo

**Adriana Dawes**
Ohio State University, Columbus, OH, USA

Single cell embryos of the nematode worm Caenorhabditis elegans polarize by segregating specific types of proteins called Par proteins to distinct domains. The boundary between these domains is reliably positioned in wild type cells, although the mechanism for boundary positioning is not well understood. In this talk, I will present a biologically based model of the Par proteins as well as a simplified model based on the perturbed Allen-Cahn equation to demonstrate how domain thickness may play a role in positioning the Par protein boundary.

**Judy Day**, University of Tennessee, Knoxville, TN, USA
Yoram Vodovotz, University of Pittsburgh, Pittsburgh, PA, USA

## The Role of T-cells in Hemorrhagic Shock

It has traditionally been thought that the immune response acts in two separate, virtually distinct phases when encountering infection or trauma: the innate immunity phase and the adaptive immunity phase. The cells in the innate immunity phase act in a general way toward the present danger and communicate appropriately to the adaptive immune players who then act in a more specific, focused way. However, the lines between these two phases can be quite blurred since T-cells, primary members of the adaptive arm, can produce many of the cytokine molecules that are produced by the cells involved in the innate response. In this way, T-cells can augment or regulate the response of the "innate arm" of the response.

In the work of Torres et al. 2009, experimental and modeling work was carried out to examine the cascade of immune events triggered by a drastic loss of blood over a relatively short period of time. At the time, it was not widely accepted that T-cell responses could have an earlier effect on some of the typical "innate" immune response events in this scenario. Thus, the communication cascade going from the innate mediators (e.g. macrophages) to the antigen presenting cells (e.g. dendritic cells) and then to the T-cells was not considered in the work. Here we explore the role that T-cells, including T-helper cells of type 1 and 2 as well as T regulatory cells, have on the immune response effort to guard against hemorrhagic shock.

Torres A, Bentley T, Bartels J, Sarkar J, Barclay D, Namas R, Constantine G, Zamora R, Puyana JC, Vodovotz Y. Mathematical modeling of posthemorrhage inflammation in mice: studies using a novel, computer-controlled, closed-loop hemorrhage apparatus. Shock. 2009 Aug;32(2):172-8.

## Computability, Gödel's Incompleteness Theorem, and an Inherent Limit on the Predicability of Evolution

**Troy Day**
Dept. of Mathematics & Statistics, Dept. of Biology, Queen's Univ., Ontario, Canada

Abstract:
I will briefly review a main way in which mathematical modeling has been used to understand and predict evolutionary change. I will then highlight an important shortcoming of such approaches and consider an alternative that attempts to overcome the problem. This alternative encompasses what I refer to as "open-ended" evolution. I will then present a proof, using this approach, that certain evolutionary questions are inherently unanswerable unless the process of evolution has specific properties. The cause of this limitation on evolutionary theory is shown to be fundamentally the same as that underlying the Halting Problem from computability theory and Gödel's Incompleteness Theorem.

**Sandra Delgadillo,** Centro de Investigación en Matemáticas, A.C., Guanajuato, GTO. México
Francisco Solís, Centro de Investigación en Matemáticas, A.C., Guanajuato, GTO. México

## A numerical study of the evolution of an aggressive heterogeneous tumor with different chemotherapy treatments

Discrete mathematical models are proposed to study the dynamics of an aggressive heterogeneous tumor. The models include the application of a chemotherapy treatment with a gradual effect. Another factor included in the models is the competence among the different tumor cells. An effective treatment index is introduced in order to analyze the evolution of the tumor and to compare different treatments.

**Edgar Delgado-Eckert**, University Children's Hospital (UKBB), University of Basel, Basel, Switzerland.
Michael Shapiro, Department of Pathology, Tufts University, Boston, MA, USA.
Niko Beerenwinkel, Department of Biosystems Science and Engineering, Swiss Federal Institute of Technology Zurich (ETH Zürich), Basel, Switzerland.

# Epistasis on Networks: Genetic Interactions and Network Reliability

## Abstract of oral presentation

The biochemical and molecular mechanisms underlying epistatic phenomena observed in various living organisms are poorly understood. *Epistasis*, or *genetic interactions*, refers to functional relationships between genes. It describes the phenotypic effect of perturbing (e.g., knocking down or knocking out) two genes separately versus jointly relative to the unperturbed system. Thus, epistasis is a property of the underlying network of biochemical interactions in the cell. Interacting biological or biochemical entities are often represented as networks (or graphs), where vertices correspond to components (e.g., genes, proteins, or metabolites) and edges correspond to pairwise interactions (e.g., activation, molecular binding, or chemical reaction). This abstract representation provides the conceptual basis for network biology, which aims at understanding the cell's functional organization and the complex behavior of living systems through biological network analysis.

In this work, we introduce a mathematical framework linking epistatic gene interactions to the redundancy of biological networks. Our approach is based on *network reliability*, an engineering concept that allows for computing the probability of functional network operation under different network perturbations, such as the failure of specific components, which, in a genetic system, correspond to the knock-out or knock-down of specific genes. Using this framework, we provide a formal definition of epistasis in terms of network reliability and we show how this concept can be used to infer functional constraints in biological networks from observed genetic interactions.

In this talk, we will introduce the concept of epistasis on networks within the framework of probabilistic graphs. Furthermore, we will present some basic mathematical properties relating redundancy of the network under consideration and epistasis.

Moreover, we will demonstrate, using a concrete experimental data set ([2]), how our methodology can be used to infer functional and topological constraints in biological networks from observed genetic interactions.

Our formalism might help increase our understanding of the systemic properties of the cell that give rise to observed epistatic patterns.

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**Jeff Denny**, Mercer University, Macon, GA, USA
Lyndssey Autrey, Mercer University, Macon, GA, USA
Belsey Garcia, Mercer University, Macon, GA, USA
Tiet Hoang, Mercer University, Macon, GA, USA
Amy Wiles, Mercer University, Macon, GA, USA

## A Yeast Competition Lab for Teaching Mathematical Biology

This presentation will report on our work to develop a teaching exercise for undergraduate students in an upper-level mathematical biology course. Significant amounts of teaching materials have been created for mathematical biology courses at an introductory level, but more are needed at the upper-level. The goal for the exercise is to expose junior/senior-level students to the complete modeling experience from bench work to the analysis of the mathematical model. To this end, we chose to adapt the classical experiment by G. F. Gause (1934), examining the effects of competition on the growth of two species of yeasts – S. *cerevisiae* and S. *pombe* – in a limited nutrient environment. During growth and proliferation of these two yeasts, the different species must compete for nutrients while also being exposed to byproducts produced by either species. Such competition between two species vying for the same niche can be modeled with a system of two differential equations. Protocols were developed and simplified for students with limited molecular biology experience. Pure and mixed cultures of the yeasts were grown until stationary phase was reached in each culture. For the in-class bench experience, media conditions can be modified so teams of students may push species domination toward one or the other. Work is also underway to establish a pair of yeasts with required media conditions for co-existence. Having gathered biological data, students perform the mathematics portion of the lab by fitting the differential equations model to the experimental evidence and characterize the growth of the populations. Students should gain understanding in analyzing parameters and classifying equilibrium solutions.

**James Dillon, University of Scranton, Scranton, PA and NIMBioS: National Institute for Mathematical and Biological Synthesis, Knoxville, TN, USA**

**Weijie Li, Luther College, Decorah, IA and NIMBioS, Knoxville, TN, USA**

**Andre Perez, University of Texas, El Paso, TX and NIMBioS, Knoxville, TN, USA**

Juanjuan Chai, NIMBioS, Knoxville, TN, USA

Michael Gilchrist, Department of Ecology and Evolutionary Biology, University of Tennessee and NIMBioS, Knoxville, TN, USA

## Modeling protein translation and genome evolution

Protein translation, an important step in gene expression that assembles the proteins used throughout the cell, is one of the most fundamental and conserved biological processes. Yet like all biological processes translation has intrinsic costs and processing errors. Due to redundancy inherent in the genetic code (e.g. codons GAA and GAG both code for glutamic acid), the evolution of coding sequences will be influenced by these costs and errors. The goal of this summer's research be to use mathematical models of the intra-ribosomal processes responsible for the costs and errors during protein translation in order to study the patterns found within the genomes of different organisms. The outcome of this work will be a better understanding of how the ribosome works and, in turn, our ability to extract information from genomic sequences.

**This is an Undergraduate Poster

**Hana M. Dobrovolny**, Ryerson University, Toronto, ON, Canada
Keith D. Poore, Ryerson University, Toronto, ON, Canada
Catherine A.A. Beauchemin, Ryerson University, Toronto, ON, Canada

## Characterizing monotherapy and combination therapy of influenza

Two classes of antivirals are used to treat influenza infections: adamantanes, which prevent the virus from releasing its genetic material into the cell nucleus; and neuraminidase inhibitors (NAIs), which prevent newly formed virions from detaching from infected cells. Unfortunately, viral strains can become resistant to an antiviral through a single amino acid mutation, and there has been a recent rapid rise in the number of circulating viral strains that are resistant to at least one class of antivirals. In an effort to combat the emergence of resistant strains, researchers have begun to investigate combination therapy using two or sometimes three different antivirals. To determine the optimal treatment options, it is important to properly characterize the efficacy of both monotherapy and combination therapy.

Monotherapy is characterized by determining the effect of a drug as a function of the dose. This function is characterized by two parameters: the $IC_{50}$, the drug concentration needed to achieve half the maximum effect; and $\varepsilon_{max}$, the maximum possible effect of the drug. $IC_{50}$ is often measured experimentally and is used to characterize the susceptibility of a viral strain to a particular antiviral. $\varepsilon_{max}$, however, is not typically measured. We use mathematical models of influenza infections to determine both the $IC_{50}$ and $\varepsilon_{max}$ of oseltamivir, the most commonly used NAI, from experimental infections. We then use the models to investigate the role of both $IC_{50}$ and $\varepsilon_{max}$ in characterizing the efficacy of NAI treatment and show that $\varepsilon_{max}$ is just as important as $IC_{50}$ in characterizing the efficacy of the drug.

We then combine the results of our analysis of oseltamivir with analysis results of a similar experiment using amantadine to evaluate combination therapy. Combination therapy is characterized by determining whether certain dose combinations of two drugs are synergistic, when the combined effect of the drugs is greater than the sum of the individual effects, or antagonistic, when the combined effect of the drugs is less than the sum of the individual effects. Our models predict that oseltamivir and amantadine will combine synergistically for some dose combinations, but that the location of the synergistic region depends on the measurement time. Additionally, we find that the synergistic region does not necessarily occur for doses that suppress the infection, calling into question the relevance of synergy.

Our results suggest that current methods of characterizing the efficacy of drug treatment of influenza are inadequate. In the case of monotherapy, $\varepsilon_{max}$ should routinely be measured in addition to $IC_{50}$ in order to completely characterize a viral strain's susceptibility to a drug. In the case of combination therapy, we find that synergy is an inadequate measure to characterize the efficacy of the treatment because it is dependent on measurement time and because it does not measure the actual efficacy of the treatment.

**Tyler Drake**, Department of Physics, Lehigh University, Bethlehem, PA, USA
Dimitrios Vavylonis, Department of Physics, Lehigh University, Bethlehem, PA, USA

## A Model of Fission-Yeast Cell Shape Driven by Membrane-Bound Growth Factors

Fission yeast serves as a model for how cellular polarization machinery is used to regulate cell growth. Many studies identify active Cdc42, found in a cap at the inner membrane of growing tips, as an important growth regulator, likely through control of exocyst tethering and the targeting of other polarity-enhancing structures. To investigate how these molecular processes might control shape, we propose a simple model based on the hypotheses that (i) the delivery and internalization rate of wall or membrane components limits cell expansion and (ii) a growth factor, such as Cdc42, signals for delivery of these components. We numerically simulate cell growth according to an axisymmetric, finite-element computational model of growth-factor-directed cell-wall remodeling under turgor pressure. We find relationships between signal profile and cell shape, and motivate future experiments on the link between cell signaling and shape.

Fission yeast is a model organism for cell shape in part because of the numerous identifiable shape mutants. Deletion of many Cdc42 regulators leads to defects in shape or polarized growth, such as cells of varying diameter, round cells, and branched cells. We consider the roles of auxiliary proteins, incorporate findings on length-dependent polarity change, compare model results to cell morphologies of mutants of Cdc42 regulators, and suggest possible mechanistic roles for these regulators. Finally, we describe a model that includes three simple interacting modules and can reproduce many known shape mutants using reasonable assumptions about the mechanistic roles of the regulating proteins.

## Polarized Stochastic Amplification During Mating in *Saccharomyces cerevisiae*

**Brian Drawert**[1,3], Michael Lawson[1], Mustafa Khammash[1,2], Linda Petzold[1], Tau-Mu Yi[1]
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**Keywords:** Systems biology, Computational biology, Molecular biology, Cell biology

We have developed a spatial stochastic model of polarisome formation in mating yeast, focusing on the tight localization of proteins on the membrane. This new model is built on simple mechanistic components, but is able to achieve a highly polarized phenotype with a relatively shallow input gradient. Preliminary results highlight the need for spatial stochastic modeling and simulation to reproduce experimental observations.

One of the best-studied examples of cell polarization is the growth of the mating projection during yeast mating. Yeast cells localize specific proteins to the front of the cell in response to a spatial gradient of mating pheromone secreted by a partner [1]. The spatial sensing and response exhibit remarkable sensitivity, dynamic range, and robustness. A single molecular entity located at the front of the cell, termed the polarisome, helps to organize structural, transport, and signaling proteins [2]. The function of the polarisome is well-conserved in eukaryotes, and analogous scaffold complexes may be responsible for such diverse structures as focal adhesions and synapses [3].

Prior work has produced deterministic (PDE) mathematical models that described the spatial dynamics of yeast cell polarization in response to spatial gradients of mating pheromone [4], as well as addressing the trade-off between amplification and tracking [5]. Noise plays an increasingly acknowledged role in intra- and intercellular signal transduction, protein interaction networks, and gene regulation [6], and as such, increased focus has been placed on developing stochastic models of biological systems. Recently, models of self-recruitment [7] and actin nucleation and directed transport [8] have highlighted the important role of spatial stochastics in initializing and maintaining polarization in the absence of an external cue.

In this work, we present a model that combines gradient-sensing, directed transport and self-recruitment and also focuses on three molecular species: Bni1 (a formin that nucleates actin [9]), Spa2 (a scaffold protein), and actin. The mechanisms and rate constants in this model are based on evidence from the literature [2,9-10] and experiments.

Stochastic simulation of our model reproduces the sharp polarization seen in experiments, whereas deterministic simulation fails to achieve tight spatio-temporal localization. In addition, stochastic simulation is required to balance tight polarization and the dynamic searching behavior that allows for the tracking of the input cue. We show that spatial stochastic models are necessary to reproduce these biological phenomena with mechanisms that are simple and biologically relevant.

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**Carolyn Drobak**, St. Jude Children's Research Hospital, Memphis, TN, USA; Rhodes College, Memphis, TN, USA
Erin Bodine, Rhodes College, Memphis, TN, USA
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## Modeling the Hypothalamic Pituitary Adrenal Axis System for Dexamethasone Treatment

The hypothalamic pituitary adrenal axis (HPA) system regulates stress in the brain. When this system experiences a dysfunction, such as during chemotherapy treatments, there can be a number of unwanted side-effects such as depression or chronic fatigue syndrome. Dexamethasone (Dex) is a pharmaceutical drug used to lessen side-effects of some cancer treatments and to prevent some HPA dysfunctions. In this study, we adapt a system of nonlinear ordinary differential equations for the HPA system to account for the administration of Dex. We propose a simplified system which focuses on the hormone and receptors directly affected by Dex. Uncertainty analysis is used to see how changes in parameter values effect the output of both the full and simplified systems as a whole, while sensitivity analysis is used to determine how sensitive the model is to these small parameter changes. Additionally, equilibria for the simplified model are found numerically. In the parameter sets explored, the equilibrium is stable.

**Vanja Dukic**, University of Colorado, Boulder, CO, USA

## Bayesian Modeling of Smoking Exposure During Pregnancy

Studies trying to assess effects of prenatal exposure to cigarettes frequently acquire both self-report and biologic assays of maternal smoking. Most common biological assays are those of cotinine, a metabolite of nicotine, from urine or serum. Both of those measures have their own sources of information and bias. Single bioassay measures alone cannot reflect the metabolic mechanism over time, while self-report may have serious recall, topographic, and metabolic biases. In this project we present a Bayesian statistical model for describing in utero smoking exposure based on the combined biological and self-report information. The model takes into account heterogeneity among women and metabolism during pregnancy. The model is applied to the data from East Boston Family Study.

**Christine Dumoulin**, The University of Tennessee, Knoxville, TN, USA
Austin Milt, The University of Tennessee, Knoxville, TN, USA
Paul Armsworth, The University of Tennessee, Knoxville, TN, USA

## Modeling Spatial Information Transfer Across Trophic Levels

Differences in spatial and temporal scale are inherent to many cross-species interactions. Spatial patterns formed by such interactions depend both on population processes at each species' own scale, and on the distribution of the other species. For example, predation affects the distribution of predators and prey, but the prey distribution is simultaneously affected by differences in resource availability over space.

From a signal processing standpoint, populations transform spatial environmental information by populating favorable patches, and cross-species interactions propagate information across trophic levels. We expect that disparities in perceptual grain affect the way that trophic interactions transform spatial information.

To address this question, we describe a novel variation on the lattice model. Our model consists of two interacting lattices with different resolutions, and an underlying layer of spatially explicit environmental variation. Prey populations inhabit the fine-grained lattice at the same resolution as environmental variation, while predator populations inhabit the coarse-grained lattice. Cells of the fine-scale lattice nest exactly into coarse-scale lattice cells. Predators respond to the total number of prey within each coarse cell, but cannot perceive prey populations' spatial structure on the fine-grained level.

By simulating a general predator-prey interaction at a range of scales, we explore how perceptual grain disparity distorts spatial environmental pattern as it propagates through trophic levels. We also consider implications for predator-prey coexistence, and for the ability of each species to track necessary resources as they vary across space.

## Bacterium *Pseudomonas aeruginosa* propagates as a ring to result in efficient colonization of surfaces

**Dr. Huijing Du**
Department of Mathematics, University of Notre Dame

Abstract: We observed that *P. aeruginosa* often forms branched tendril patterns during swarming and this phenomena occurs only when bacteria produce rhamnolipid, regulated by quorum sensing. We also observed that *P. aeruginosa* cells and rhamnolipid propagate as rings within swarms towards the extending tendrils. We developed a cell-based multi-scale model to study this phenomenon. Our simulations suggest that the ring propagation as well as branched tendril formation at the edge of the population depends upon competition between the changing viscosity of the bacterial liquid suspension and the liquid film boundary expansion caused by Marangoni forces. We therefore suggest that *P. aeruginosa* efficiently colonizes surfaces by controlling the physical forces responsible for expansion of thin liquid films and by propagating towards the tendril tips.

**Yimin Du**, York University, Toronto, ON, CA
Jane Heffernan, York University, Toronto, ON, CA
Jianhong Wu, York University, Toronto, ON, CA

## The basic in-host model for Tuberculosis(TB)

Tuberculosis (TB) is the number one cause of death due to infectious disease today, with over one-third of the world population infected with *M. tuberculosis* and almost 2 million TB-related deaths every year. With the HIV epidemic and the appearance of multidrug-resistant TB, TB is becoming even more deadly. TB infection results in clearance, latent infection or active disease (slow or fast progression). Only $5-10\%$ of infected individuals developing active disease in the first 5 years postinfection. Thus, studying the dynamics of immune response in TB infection is crucial to developing predictors of disease outcome. Mathematical models have been used to provide some insight into this, however, such models have been very complicated with very high dimensions (i.e. $>10$ equations). This does not compare to the simple and very powerful basic model of virus dynamics (only 3-dimension) that has been used to give great insight into the pathogenesis of various viral infections (i.e. HIV, HCV). We develop a simple 4-dimension mathematical model of TB infection in-host. The model includes macrophages, T lymphocytes, bacteria and their interactions, and captures all disease outcomes. Uncertainty and sensitivity analysis and numerical simulations have given very interesting results, including identification of key parameters that determine disease outcome, as well as model conditions which can produce a backward bifurcation. The model also provides a sound foundation for future studies on the pathogenesis of drug resistant TB and HIV/TB coinfection.

**Tripti Dutta**, York University, Toronto, Ontario, Canada
Dr. Jane Hefferenan, York University, Toronto,Ontario, Canada

## Title: Variability in HIV Infection In-host: A Monte Carlo Markov Chain Model.

HIV/AIDS is a serious threat to public health around the globe. It is estimated to have killed more that 25 million people since it was first recognized. HIV damages the immune system by targeting CD4 T-cells, the main driver of immune response. Through infection it kills these cells which make a patient susceptible to opportunistic infections. CD4 T-cell count and viral load measurements are used to assess patient health, and assess the efficacy of drug therapy. Natural fluctuations in these measurements however, can obscure clinically significant changes. We have developed a Markov Chain Monte Carlo (MCMC) stochastic simulation to measure the expected variability in viral load and T-cell count for a simple model of HIV virus dynamics. The model considers the acute and latent stages of infection and determines variability in the time to peak viral load, the magnitude of this peak, the basic reproductive ratio, the initial growth rate, and the infected equlibrium. The simulation is also used to measure the probability of extinction of an initial viral load.

**Hermann J Eberl,** University of Guelph, Guelph, ON, Canada, N1G 2W1
Vardayani Ratti, University of Guelph, Guelph, ON, Canada, N1G 2W1
Peter G Kevan, University of Guelph, Guelph, ON, Canada, N1G 2W1

## On honeybees, varroa destructor and deadly diseases: a mathematical approach

The western honeybee is in trouble. In recent years beekeepers all over Europe and North America reported drastic, unprecedented losses of colonies. Among the many stressors that were proposed, parasitic varroa mites have been identified as one of the main culprits. These mites, in addition to being harmful to the bees themselves, are also the vector for several bee viruses.

We present a simple model of the honeybee-varroa mite-acute bee paralysis virus complex. This is a system of four ordinary differential equations, the coefficients of which change with the seasons, i.e. are periodic functions of time. We study this model with a mix of analytical and numerical techniques. This will be broken down into first studying the model without mites and viruses, then the model with mites only but without viruses, and finally the complete model. We find that the bee colony is never able to fight off mites. As long as the mites are virus free we can find (realistic) conditions under which a mite infested colony can function as a seemingly healthy colony. On the other hand, if viruses are introduced, the colony will eventually vanish. An interesting observation is that although this collapse is rapid, it might occur years after the virus was originally introduced, which is consistent with beekeeper reports. We also are able to find a conditions on the model parameters under which the bee colony is able to fight off the virus. The range of parameters needed for this, however, is not necessarily realistic.

**Heiko Enderling**, Lynn Hlatky, Philip Hahnfeldt

Center of Cancer Systems Biology, St. Elizabeth's Medical Center, Tufts University School of Medicine, 736 Cambridge Street, Boston MA, 02135, USA

## The promoting role of a tumor-secreted chemorepellent in self-metastatic tumor progression

It has been proposed that cancer cells, in particular glioma tumor cells, secrete a chemorepellent factor that guides cell migration away from the tumor, facilitating migration and invasion. We present a hybrid continuous discrete mathematical model of tumor growth and the chemotropism phenomenon to show that such a chemorepellent factor can also act as a promoter of self-metastasis, a mechanism for tumor expansion we have previously shown can explain several essential kinetic dependencies of tumor growth. A sufficient criterion for this expansion was found to be the passive migration of peripheral cancer stem and non-stem cells away from the main tumor mass. The migrating cancer stem cells formed new clusters while simultaneously releasing neighboring quiescent cancer cells to proliferate and form new progeny. We show here how the introduction of an active repellent trait serves to accelerate peripheral migration, and thus, by the self-metastasis principle, accelerate tumor growth. These results provide a mechanistic basis for the proposal that chemorepellent action in gliomas may underlie their rapid growth.

**Roger Fan**, Undergraduate, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
Faculty Advisor: Dr. Laura Miller

## Modeling the Electrophysiology of Jellyfish Using the FitzHugh-Nagumo Equations

Jellyfish are among the simplest animals that possess a true nervous system. The primitive jellyfish nervous system is called a nerve net. Nerve nets are involved in the control of muscles, which are used for pumping water. Pumping water serves a number of purposes, such as swimming, feeding, and decelerating during descent.

The nerve nets of jellyfish synapse with pacemaker structures. Pacemakers are capable of depolarizing without receiving an external stimulus. These pacemakers set the pulsing rhythm for muscle contractions. Jellyfish seldom remain at a constant pulsing frequency; changes in the frequency can be erratic for a single specimen. Frequency also tends to vary by size as large jellyfish tend to pump slower than small jellyfish.

The dynamics of the nerve net neurons can be modeled by the FitzHugh-Nagumo equations. The FitzHugh-Nagumo equations are a simplification of the Hodgkin-Huxley model for nerve impulses. By incorporating a diffusion term, action potentials can be shown to spread in two-dimensional space. There are two main types of nerve nets found in jellyfish: the motor nerve net and the diffuse nerve net. The motor nerve net can be conceived as an annulus in two-dimensional space. A single signal can spread bi-directionally around the ring until it cancels itself at the halfway point. The diffuse nerve net can be represented by a circle. Signals on the diffuse nerve net will spread isotropically until reaching the boundaries. The motor and diffuse nerve nets both interface with pacemakers. Information from both nerve nets is thought to influence the depolarization of pacemakers.

This model demonstrates many of the features and phenomena observed in the electrophysiology of jellyfish. It can be shown that high-frequency pacemakers tend to dominate over slower pacemakers. This model can exhibit the fast conducting action potentials of the motor nerve net as well as the slow conducting action potentials of the diffuse nerve net.

## Optimal Control in Individual Based Models: Implications from Aggregated Methods

**Paula Federico***, Louis Gross, Suzanne Lenhart, Daniel Ryan
*Department of Mathematics, Computer Science and Physics, Capital University, Bexley, Ohio

The hypothesis we investigate is whether optimal control theory applied to an aggregated model (AM) of differential equations can be used to effectively control a harmful species modeled by an Individual-based Model (IBM), or whether interactions between individuals, their spatial distribution, and landscape heterogeneities limit the effectiveness of the control methods derived from the aggregated model. We develop a simple spatially explicit IBM with an invasive species (rabbits) and its resource (grass). Then we formulate a differential equation model for the rabbits and the grass to mimic the average time dynamics of the IBM, and choose appropriate parameters. We find an optimal control based upon harvesting the "harmful" species in the AM. This control is then applied to the IBM, and the results from both models with control are compared. We first investigate situations with no spatial heterogeneity in the resource (except stochastic fluctuations), and then investigate a situation with explicit spatial heterogeneity in the resource. The optimal control derived from the AM can be used effectively to control the invasive species in the IBM in the former situation for most of the parameter space. However in the case of an explicit strong spatial heterogeneity in the resource, the AM optimal control becomes inefficient even though the AM with no control closely captures the average dynamic of the IBM.

**Kimberly Fessel**, Rensselaer Polytechnic Institute, Troy, NY, USA
Mark H. Holmes, Rensselaer Polytechnic Institute, Troy, NY, USA

## The Nonlinear Effects of Electromotility in the Inner Ear

Sound is received and processed by mammals via mechanotransduction of traveling waves in the cochlea. Though numerous successful linear math models have been developed to describe cochlear mechanics, many significant nonlinearities exist in the traveling wave and have not been explained. Outer hair cell electromotility is the primary source of a majority of these nonlinearities. Resulting from sound stimulation and subsequent shifts in the cells' receptor potentials, electromotility is the process by which outer hair cells undergo conformational length changes. In this work, a model for electromotility will be derived, and its nonlinear effects on the traveling wave will be analyzed.

**Edward Flach**, Moffitt Cancer Centre, Tampa, Florida, United States of America

## Evolutionary model gives strategy for targeted cancer therapies

Targeted drug treatment reduces tumour volume, but sadly there is almost always recurrence. We propose a simple model to understand this mechanism. We see that each cancer consists of a diverse population of cell phenotypes. However, the diversity of these phenotypes has a limited range, and we model this. We use targeted therapy on multiple cell lines: the treatment fails because of the diversity within the cancer. We fit our model to this experimental behaviour. A second experiment shows that drug sensitivity returns in a treatment holiday. The experiment shows further that our cancer cell line consists of distinct sub-populations. The fundamental effect of the targeted therapy is to eradicate some of the sub-populations. Extending our model, we see that combination therapies fail when resistant landscapes overlap. In contrast, combination therapies will succeed when resistant landscapes are distinct.

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## BioCellion: A High-performance Computing Framework for Multiscale Modeling and Simulation of Multicellular Biological Systems

Modeling and simulation of large-scale biological systems is becoming essential in the support of high-throughput experiments and the discovery and evaluation of therapies. As the need grows for higher fidelity models that couple micro, meso and macro scale subsystems, the computational resources required are emerging as the key limitation preventing advancement. This work describes a new modeling software framework specifically designed for rapid simulation of large scale biological models that span multiple embedded scales. BioCellion utilizes high-performance computing up to petascale supercomputers ($10^{15}$ floating point operations per second) and can simulate complex systems of billions or more cells.

BioCellion is a hybrid multicellular modeling system where biomechanical mechanisms are represented through local spatial interactions of off-lattice particles, domain scale biomolecular interactions through PDEs and intracellular regulation through ODE and/or Boolean biomolecular networks. BioCellion supports alternative levels of cellular abstraction where a cell can be represented as a single spherical particle or as a contiguous cloud of interacting particles (the sub-cellular model).

BioCellion is currently being applied to investigate a diversity of prokaryotic and eukaryotic cellular systems: biofilm-like development of yeast colonies, breast cancer micro-tumor interactions between growth and extracellular matrix degradation, the formation and homeostasis of complex thermophilic bacterial colonies, and the morphodynamics of vascularization. To support diverse model specification, a set of generic cellular mechanisms has been implemented including regulated growth and division, differential adhesion, reaction and diffusion, contact mediated signaling, contact inhibition, extracellular secretion and degradation, and chemotaxis.

BioCellion is intended to be a resource for the biological modeling community. Specific biological systems are specified using a combination of XML when utilizing mechanisms previously implemented, combined with customized c-language plugins for new mechanisms. Specialized knowledge of high-performance computing is not necessary. XML instantiations support the definition of the model domain, initial conditions, and cell type physiology as intracellular regulatory networks coupled to configurations of cellular mechanisms. A public repository of models and mechanisms will be built to enable active collaboration among modelers.

The aim of this talk is to introduce BioCellion to the broader modeling community, demonstrate its capabilities using examples from a diversity of multicellular systems and invite researchers to be part of the project as it develops.

**Cesar O. Flores**, School of Physics, Georgia Institute of Technology, Atlanta, GA, USA
Sergi Valverde , Complex Systems Lab and Institute of Evolutionary Biology, University Pompeu Fabra, Barcelona, Spain
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## Phage-Bacteria Interaction Networks: From Nestedness to Modularity

Bacteriophages (viruses that infect bacteria) are the most abundant biological life-forms on Earth. However, very little is known regarding the structure of phage-bacteria infections. In a recent study we showed that phage-bacteria infection assay datasets are statistically nested in small scale communities while modularity is not statistically present (Flores et al 2011). We predicted that at large macroevolutionary scales, phage-bacteria infection assay datasets should be typified by a modular structure, even if there is nested structure at smaller scales. We evaluate and confirm this hypothesis using the largest study of the kind to date (Moebus and Nattkemper 1981).

The study in question represents a phage-bacteria infection assay dataset in the Atlantic Ocean region between the European continental shelf and the Sargasso Sea. We present here a digitized version of this study that consist of a bipartite network with 286 bacteria and 215 phages including 1332 positive interactions, together with an exhaustive structural analysis of this network. We evaluated the modularity and nestedness of the network and its communities using a variety of algorithms including BRIM (Bipartite, Recursively Induced Modules), NTC (Nestedness Temperature Calculator) and NODF (Nestedness Metric based on Overlap and Decreasing Filling). We also developed extensions of these standard methods to identify multi-scale structure in large phage-bacteria interaction datasets. In addition, we performed an analysis of the degree of geographical diversity and specialization among all the hosts and phages.

We find that the Moebus and Nattkemper (1981) study, as anticipated by Flores et al. (2011), is highly modular and not significantly nested (computed in comparison to null models). More importantly is the fact that some of the communities extracted from Moebus and Nattkemper dataset were found to be nested. We examine the role of geography in driving these modular patterns and find evidence that phage-bacteria interactions can exhibit strong similarity despite large distances between sites. We discuss how models can help determine how coevolutionary dynamics between strains, within a site and across sites, drives the emergence of nested, modular and other complex phage-bacteria interaction networks

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**Jonathan Forde**, Hobart and William Smith Colleges, Geneva, NY, USA
Yaoxin Liu, Hobart and William Smith Colleges, Geneva, NY, USA
Yixiao Sha, Hobart and William Smith Colleges, Geneva, NY, USA

## Mathematical Models of the Role of Immune Exhaustion in Hepatitis B and Delta Coinfection

Hepatitis Delta Virus (HDV) is a dependent satellite virus of the more common Hepatitis B Virus. HDV encodes only one protein of its own, relying on HBV to supply the additional proteins needed for its replication cycle. Although it HDV is noncytotoxic and present few targets for immune reaction, the symptoms of patients with HBV-HDV coinfection are much worse than those infected with HBV alone. The cause of this negative outcome is not clear. This work presents o.d.e. models for the interaction of HBV, HDV and the specific immune responses to each, and analyzes the implication of these models for understanding patient outcomes. In particular, the role of T cell exhaustion in chronic HBV is explored, and how superinfection with HDV may actually strengthen the HBV specific immune response, indirectly leading to the observed symptoms. Additionally, the role of nonspecific immune responses is explored.

**Rachel Fovargue**, University of Tennessee, Knoxville, TN, USA
Paul Armsworth, University of Tennessee, Knoxville, TN, USA
Michael Bode, University of Melbourne, Melbourne, VIC, Australia

## Managing Reef Fish under Stochastic Dispersal Conditions

Effective placement of marine protected areas (MPAs) in the Great Barrier Reef (GBR) may be vital for maintaining fishable populations. The success of MPAs depends in part on reef connectivity and larvae dispersal patterns. Because ocean currents in the GBR are complex and dynamic, managers are challenged to place MPAs that maintain fish abundance over the long run. One strategy to improve management efforts is to cluster bordering reefs into several distinct MPAs. Placing MPAs as clusters of reefs may allow for local larval dispersal patterns to successfully seed reefs under a variety of ocean conditions Here I use a single-species metapopulation model of the GBR to test how the size and number of MPAs affects mean fish abundance and fishery catch levels. I find that under a constant total protected area there is an increase in mean fish abundance and decrease in variance as the number of distinct MPAs increases. I also compare this pattern across different amounts of total reef area protected (10%, 20%, 30%, 40% of the GBR) and find that cluster size may have a more profound impact on fishery catch than fish abundance as MPAs make up a higher proportion of the reef.

**John Fricks**, Pennsylvania State University, University Park, PA, USA

## Microtubule-Based Transport by Multiple Identical Molecular Motors.

A system of stochastic differential equations (SDEs) is used to model the interaction between processive molecular motors, such as kinesin and dynein, and the biomolecular cargo they tow as part of microtubule-based intracellular transport. Moreover, the classical experimental fluid environment fits within a parameter regime which is qualitatively distinct from conditions one expects to find in living cells. Through an asymptotic analysis of our system of SDEs, a means for applying *in vitro* observations of the nonlinear response by motors to forces induced on the attached cargo is developed to make analytical predictions for two parameter regimes that have thus far eluded direct experimental observation: 1) highly viscous *in vivo* transport and 2) dynamics when multiple identical motors are attached to the cargo and microtubule. Time permitting, the connections between the model described and models at the single motor level will be discussed.

**Brendan C. Fry**[1], Timothy W. Secomb[1,2]
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## Simulation of Metabolic Blood Flow Regulation by Wall-Derived and Red-Blood-Cell-Derived Mechanisms: Responses to Hemodilution

Oxygen exchange between blood and tissue occurs primarily in the microcirculation, which has a heterogeneous structure with wide variation in vessel geometry and flow rates. Blood flow in the microcirculation is regulated according to local metabolic demands of the tissue; however, the mechanism for this regulation is not entirely known.

The purpose of this investigation is to analyze the effects of metabolic flow regulation by signals derived from the vessel wall and derived from red blood cells, in response to a reduction in systemic hematocrit (red blood cell volume fraction). A theoretical model is used to simulate blood flow, oxygen transport, and flow regulation in microvascular networks with realistic heterogeneous structures. Flow regulation is modeled based on length-tension characteristics of vascular smooth muscle, and includes myogenic, shear-dependent, and metabolic responses. If the hematocrit is reduced (hemodilution), the initial effects (before active diameter changes) are increased blood flow rates due to the reduction in apparent viscosity, but decreased red blood cell fluxes. If the metabolic signal is assumed to originate solely from a red-blood-cell-dependent mechanism, the model predicts that flow regulation will then cause a reduction in blood flows and further decreases in red blood cell fluxes. If the metabolic signal is assumed to originate instead from a vessel-wall-dependent mechanism, flow regulation causes a further increase in flow, such that the initial decrease in red blood cell flux is partially reversed. These findings suggest that a red-blood-cell-independent mechanism of metabolic flow regulation is required for an appropriate physiological response to hemodilution. Supported by NIH grant HL070657.

Heinrich Freistühler, University of Constance, Konstanz, Germany
**Jan Fuhrmann**, University of Heidelberg, Heidelberg, Germany
Angela Stevens, University of Münster, Münster, Germany

## Emerging Polymerization Fronts in a Minimal Cytoskeleton Model

The directed motion of eucaryotic cells plays a major role in biological processes as diverse as wound healing, cancer metastasis, immune response, the hunting behavior of different bacteria, and many more. The common driving force of these forms of cell motility is the permanent reorganization and filament turnover of the actin cytoskeleton.
In this presentation we will derive a minimal model for the cytoskeleton of a potentially motile cell being at rest and turned into motion upon some stimulus. The model is comprised of four hyperbolic partial differential equations describing the densities of actin filament tips and one parabolic equation for the actin monomer concentration. These are coupled via the polymerization and depolymerization of monomers at the filamend ends.
We will deduce a free boundary problem for this system where the moving boundary represents the cell membrane which is supported by actin filaments and may be displaced upon their growth or shrinkage.
For this problem we show existence and uniqueness of solutions for small times. Remarkably we cannot easily rule out the emergence of Dirac measure type solutions to the hyperbolic equations together with discontinuities in the monomer concentration – a phenomenon known as interior gradient blow-up.
In fact, the investigation of the hyperbolic limit system without diffusion of monomers reveals possible discontinuous solutions which can be found analytically. Numerical results suggest that at least the local concentration of large numbers of filament ends also occur in the original model with diffusion.
We furthermore find some examples of another type of shock like solutions to the full system with diffusion which are characterized by measure valued filament end densities as well but without exhibiting discontinuities in the monomer concentration.
Morover, we shall provide some numerical results illustrating the evolution of these shocks and comment on their interpretation as moving fronts of polymerizing actin filaments.
Finally, we will also show some simulations where cells are turned into movement with or without the emergence of sharp fronts depending on the particular parameter settings.

**Jonah Galeota-Sprung**, Davidson College, Davidson, NC, USA
**Andrew Lantz,** Davidson College, Davidson, NC, USA
**Tucker Whitesides,** Davidson College, Davidson, NC, USA
Laurie Heyer, Davidson College, Davidson, NC, USA

## Exploring Emergent Behavior in Oscillatory Systems Using Agent-Based Modeling

The field of agent-based modeling is a relatively young field of research in which researchers define sets of agents and sets of rules that control their interactions with each other and the environment. The researcher then takes on the role of observer, watching and analyzing the behavior that emerges in the system. Because of their emphasis on emergent properties arising from simple interactions, agent-based models (ABM's) are well suited to the modeling of complex biological systems such as gene networks.

Our group is engineering intercellular communication systems in bacteria, thereby laying a foundation for ABM's in which the agents are living cells. To validate our approach, we searched for a system that incorporated different methods of communication and produced emergent behavior. We chose the "biopixel" system, recently engineered at UCSD, due to its synthetic design that employed quorum sensing and gas-phase communication to synchronize global oscillation. The biopixels use quorum sensing within colonies to achieve oscillation, and gas-phase communication between pixels to synchronize oscillation between neighboring pixels. We model the biopixel system using the free ABM software package NetLogo, and suggest ways that living ABM's could be applied.

**Connor Gallagher & Benjamin Pote** (undergraduates, co-presenters), School of Natural Science, Hampshire College, Amherst, MA, USA
Sarah Hews (adviser), Hampshire College, Amherst, MA, USA

## Dynamical Model of Pollen Tube Tip Geometry

We develop a simple, 2 variable differential equation model for tip geometry in a growing pollen tube to explore a possible mechanism for oscillatory behavior. For model parameterization we use Fourier transforms to determine the dominant frequency of tube growth rate oscillations, maximum overlap discrete wavelet transforms to clean up frequency domain data, and an analytic wavelet transform to determine signal mobility and stability. The model achieves a close fit with experimental data, preserves tip dynamics, and proposes that a moving point of maximal cell wall expansion may drive oscillations in tip shape.

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## Bridging scales: combining population statistics with tissue dynamics to link primary and metastatic disease

To provide a better understanding of the relationship between primary tumor growth rates and metastatic burden, we present a method that combines population-level incidence data and tissue level growth dynamics. At the population level, we utilize a Monte Carlo simulation model of clinical cancer stage progression that was fit to the NCI Surveillance, Epidemiology, and End Results (SEER) database. At the tissue level, we use a system of partial differential equations (PDEs) to develop a spatio-temporal model of tumor growth and invasion based on the angiogenic cascade. By coupling models from both scales, the population scale metastatic burden can be explained in terms of the primary tumor vascular response and circulating tumor cell (CTC) fraction.

The population model suggests that lung tumors grow faster and shed a significant number of cells into the circulation at small sizes, whereas breast tumors grow slower and do not significantly shed cells until becoming larger. The PDE model can recapitulate these results but reveals a more dynamical relationship between the primary tumor and the CTCs. Both the PDE model and the statistical model predict exponential growth for the metastatic burden, however, there is some disparity over the primary tumor dynamics. With adequate blood supply the primary grows exponentially, but this cannot be sustained when vasculature is limited. The latter case is better correlated with power law growth. By modifying parameters in the PDE model we can account for different primary tumor dynamics that subsequently lead to different growth dynamics of the CTCs.

The vascular response is the key, both driving growth and connecting the primary tumor to metastatic burden. Whilst we do not explicitly model the metastatic population, we are able to disengage the direct dependency of the metastatic burden on primary tumor growth by introducing the CTC population as an intermediary. These results also highlight the need for pathological attributes of both primary tumor and metastases to be incorporated in databases such as SEER.

**Xuefeng Gao**, Center of Cancer Systems Biology, St. Elizabeth's Medical Center of Boston, Tufts University School of Medicine, Boston, MA, USA

## The role of cancer stem cells in radiation response of glioblastoma multiforme

Glioblastoma multiforme (GBM) is one of the most aggressive human malignancies with a dismal prognosis. Ionizing radiation (IR) is a standard therapy for GBM but remains only palliative because of radioresistance and tumor recurrence. The mechanisms underlying tumor radioresistance are manifold and, in part, accredited to a special subpopulation of tumorigenic cells. The so-called glioma stem cells (GSCs) are bestowed with the exclusive ability to self-renew and repopulate the tumor. GSCs are reported less sensitive to radiation-induced damage through preferential activation of DNA damage checkpoint responses and increase in DNA damage repair. During every boost of radiation GSCs become enriched and increase in number as the competing non-stem counterparts die, which leads to accelerated repopulation. We present a cellular Potts model that simulates glioma growth and radiation response. We parameterize and calibrate this model though in vitro experiments of U87-MG human glioblastoma cell line. Simulations reveal the kinetics underlying tumor radiation response and accelerated repopulation that yields aggressive recurrence. Potential GSC-associated mechanisms are analyzed in contributing the radiation-induced repulse of GBM including higher radioresistant and asymmetric division loss.

**Weihua Geng**, University of Alabama, Tuscaloosa, AL, USA
Robert Krasny, University of Michigan, Ann Arbor, MI, USA

## Treecode-Accelerated Boundary Integral Poisson-Boltzmann Solver

Solvation of biomolecules is a challenging problem in computational biophysics. Models that track explicit solvent molecules are extremely costly, and implicit solvent models based on the Poisson-Boltzmann (PB) equation provide an efficient alternative for computing solvent-solute interactions. Even so, PB solvers still encounter numerical difficulties stemming from the discontinuous dielectric constant across the molecular surface, the boundary condition at spatial infinity, and the presence of charge singularities representing the biomolecule. To address these issues, we present a linear PB solver employing a well-conditioned boundary integral formulation and GMRES iteration accelerated by a treecode algorithm. The accuracy and efficiency of the method are assessed for the Kirkwood sphere and a solvated protein (PDB:1A63). We compare numerical results for both the Poisson-Boltzmann and Poisson equations, using the proposed treecode-accelerated boundary integral solver, as well as the mesh-based Adaptive Poisson-Boltzmann (APBS) method. The present scheme has the features of relatively simple implementation, efficient memory usage, and straightforward parallelization.

**Estee George, Sarah Ritchey**, Youngstown State University (YSU), Youngstown, OH, USA
Robert DeVita, Youngstown State University (YSU), Youngstown, OH, USA
Gary Walker, Department of Biology, YSU, Youngstown, OH, USA
George T. Yates, Department of Mathematics, YSU, Youngstown, OH, USA

## Modeling Butanol Production by *Clostridium beijerinckii*

Although fossil fuels are currently the most economical source of energy, many other alternative energy sources are being explored as replacements for fossil fuels. Currently, millions of dollars are being spent on ethanol research. However, ethanol's energy content is only two-thirds that of gasoline. Butanol, another alternative biofuel, has similar energy content when compared to gasoline and has been gaining attention. The class *Clostridia* is known to contain species that carry out butanol fermentation from a variety of 5 and 6 carbon sugars. *Clostridium beijerinckii* is well known for its ability to grow in easily facilitated, inexpensive media and its ability to produce butanol well into the stationary phase of growth. However, butanol is known to be toxic to the bacteria in larger amounts, inhibiting growth and often lysing the cell membrane. Although butanol is miscible up to roughly 70g/L with water, standard batch fermentations only yield around 25g/L.

Experiments were conducted using the bacterium *C. beijerinckii* in 1-L screw-top shaker flasks filled with 500mL of xylose media. Samples were taken at 24, 48, and 72 hours during the experiment. Turbidity measurements were taken at each time interval. The supernatant was separated from the pellet in each sample and was analyzed to measure the substrate and solvent concentrations using high performance liquid chromatography. Cell pellets were stored at $-15$ degrees Celsius and were examined by 2DGE to determine differential protein expression. The data shows declining sugar concentrations and increasing production of acetic and butyric acid in the early part of the growth cycle and butanol production in the later part of the growth cycle.

The fermentation process is modeled by a system of differential equations based on metabolic reactions using Michaelis Menten enzyme kinetics. The equations, built from those of previously published models, are analyzed and numerically solved to explore the efficient conversion of glucose and xylose into butanol by these bacteria. The mathematical model predicts the concentrations of intermediaries and products formed throughout the course of each experimental run, and results are compared to experimental data. Each reaction equation represents the result of enzymes binding to a substrate or an intermediary to create another intermediary or one of the final products. Parameters and initial conditions are altered to best fit experimental data, and numerical simulations are represented visually in concentration versus time graphs. Results from the model are analyzed and compare favorably to experimental data. The goal of this analysis and experimentation was to find the necessary conditions for optimum yields of butanol production.

**Undergraduate Poster Session**

# Effect of immunological defense against vector on disease transmission in Bird malaria

**Suma Ghosh,** Fredrick R Adler
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Many infectious diseases are caused by parasites and pathogens that are vectored by insects. The evolution of insect-transmitted parasites is shaped by interactions with both vertebrate and insect hosts. Pigeons have many parasites in the wild; however, our study focuses on two of these parasites: hippoboscid fly – the macroparasite and a malaria parasite: *Haemoproteus columbae* – the microparasite and their interactions with the pigeon and the interaction between them. Malaria in birds can be a serious parasitic disease, as it often is in humans. Some birds die from the infection while others spread it. Hippoboscid flies take their blood meals from pigeons, which are often infected with malaria. The fly then acts as a vector, transferring malaria between bird hosts. The malaria parasite must undergo a sexual reproductive stage in the fly and an asexual reproductive stage in the bird to complete its life cycle, thus potentially impacting the fitness of both the bird and the fly. Pigeons make antibodies to flies when exposed to biting supported by the experimental data which shows the change in antibody level, measured as "optical density". The birds with flies in their backpack have significantly greater changes in their fly-specific antibody levels when exposed to flies. As pigeons develop fly antibodies, this has an impact on the transmission of flies and consequently on the disease prevalence. Also the disease prevalence depending on the fly transmission has a feedback on the persistence of fly population.

We are investigating the system from two perspectives through mathematical modelling. From the parasitic fly's point of view we are interested in the effects of malaria on fly fitness. Understanding whether malaria impacts the fitness of its vector, has implications for the transmission dynamics of malaria and possibly other vectored pathogens. From the host's point of view we are interested in how hosts combat parasites immunologically. In this project we have seen host immunological defenses against vector affect vector transmission as well as its colonization with the host which in turn affects the disease prevalence and fly population size. This study has a resemblance with the vector borne diseases of human malaria. This is also relevant to understand the vector dynamics in disease transmission and implementing control strategies through anti-vector vaccines designed to target the vectors in such a way that they protect against vector feeding and so pathogens transmitted by the vector – which is a new approach.

**Michael A. Gilchrist**, University of Tennessee, Knoxville, TN, USA; National Institute for Mathematical and Biological Synthesis, Knoxville, TN, USA
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## Using mathematical models of ribosome movement and allele fixation to extract information on protein translation from genomic datasets

Due to the inherent redundancy in the genetic code, there are a multitude of aways of coding for any given protein. Often organisms are biased in which codons they use for a particular amino acid. This codon usage bias (CUB) is most evident in, but not restricted to, highly expressed genes. The nature of this bias is generally thought to be caused by natural selection for greater efficiency in producing functional proteins. However, how different codons lead to different translational efficiencies is hotly debated. In this study we present two models that related codon usage to translational efficiency and demonstrate how these models can be used to predict gene expression levels for individual genes based on their codon bias and/or estimate the relative efficiencies of different synonymous codons. This work differs from most studies of CUB in the analysis is based on mathematical descriptions of cellular and evolutionary processes.

**Antonio J. Golubski**, Kennesaw State University, Kennesaw, GA
Edward B. Baskerville, University of Michigan, Ann Arbor, MI
Mercedes Pascual, University of Michigan & Howard Hughes Medical Institute, Ann Arbor, MI

## Food web effects of different types of interaction modifications

When ecologists model the dynamics of large communities, they most commonly use food web models. These omit widespread and important non-trophic interactions, including (for example) those resulting from adaptive behavior, or many types of mutualistic benefits. Interaction modifications (IMs), which allow the magnitude of a direct interaction between two species to be affected by the density of a third, may be used to incorporate a variety of non-trophic interactions into large food web models. However, the tractability and appropriateness of this approach will depend upon the results' sensitivity to the degree abstraction of the biological details of each IM-generating mechanism. Models attempting to fully reflect the diversity of biological mechanisms behind IMs would be prohibitively complex, yet the effects of omitting such detail on model predictions are poorly understood.

Here, we explore how sensitive the effects of IMs on food web assembly models are to the assumptions used to create IMs and place them in the web. Our goal is to gain mechanistic insight into how IMs affect food web dynamics, and better understand the consequences of omitting distinct aspects of different types of IMs in order to model them under a common framework. We examine how the effects of IMs differ when comparing IMs of different sign (i.e. IMs that strengthen interactions versus IMs that weaken them), IMs with different functional forms, or IMs whose arrangement within the web is subject to all, none, or some of the structural constraints implied by adaptive foraging as the mechanism causing the IMs.

Some promising generalities did emerge. Strengthening IMs were more likely to promote coexistence when species' persistence tended to be limited by bottom-up factors (i.e. consumers could not obtain enough energy), while weakening IMs promoted coexistence when top-down factors (i.e. prey experienced too high predation pressure) were more important. These results were robust across models with different IM functional forms and different assumptions as to how IMs interacted when affecting a common link. Similarly, weakening but not strengthening IMs were capable of stabilizing a food web motif representing apparent competition (which is prone to losing a resource species), and that motif was found to be internally stable more often in the model with weakening IMs. Finally, we found that random IMs often had opposite effects on food web parameters than did otherwise similar IMs which were structured according to an adaptive foraging model (which in our case implied that all resources consumed by a given adaptive forager strengthen all of that forager's interactions, and all predators of that forager weaken all of its interactions). However, the effects of IMs which retained some but not all of the structural constraints implied by adaptive foraging were generally more similar to those of the adaptive foraging model, suggesting that those separate elements could yield some insight into the full model's effects. In all models, IM effects could again be partially explained by the overall degree to which IMs tended to strengthen versus weaken interactions.

These models highlight both how the implications of IMs can be drastically different depending upon the assumptions underlying them, and how some of their implications might nevertheless be mechanistically understandable in terms of some of their coarser features. Neither ignoring the biological details of distinct non-trophic interactions nor omitting non-trophic interactions from food web models due to their complexity is a desirable option. It is therefore important that we continue to improve our mechanistic understanding of how various non-trophic interactions affect large food webs, and what generalities might be made concerning those effects.

**Mauricio González-Forero**, University of Tennessee, Knoxville, TN, USA

## Overview: Evolution of advanced eusociality via maternal manipulation

A notoriously extreme form of sociality is historically called advanced eusociality, where reproductives are extremely fertile and non-reproductives have highly specialized behavior or morphology. The evolution of advanced eusociality is currently explained by secondary evolution of coercion that reduces within-colony conflict which in turn favors within-colony cooperation. Here I present a model in which advanced eusociality alternatively evolves via maternal manipulation passing from a stage of conflict to one of no conflict. Maternal manipulation induces offspring to stay in the maternal site against offspring's fitness interests. Even though this creates selection pressure for resistance to manipulation, maternal manipulation also creates selection pressure for enhanced maternally controlled benefits (i.e., the mother is selected to capitalize more and more on the help available). An interpretation of maternally controlled benefits is as maternal extra fertility, which is shown to evolve to a point where Hamilton's rule is eventually satisfied. Thus, maternal manipulated helping can be stabilized in the long run by eliminating selection for resistance because of the evolution of extreme maternal fertility. Maternal manipulation can, therefore, account for two major features of advanced eusociality: non-conflictive social determination of reproductive status and extreme fertility in reproductives.

**Oscar Gonzalez**, University of Texas, Austin, TX, USA
Daiva Petkeviciute and John Maddocks, EPFL, Lausanne, Switzerland

## A Rigid-Base Model for DNA Structure Prediction

The sequence-dependent curvature and flexibility of DNA are critical for its packaging into the cell, recognition by other molecules, and conformational changes during biochemical processes. Is it possible to predict this curvature and flexibility from the basepair sequence? A model is presented which can predict these properties, and more specifically the relative position, orientation and coupling of every base in an arbitrary DNA oligomer provided it is close to the B-form structural family. The model is of the rigid-base type in which each individual base is treated as an independent rigid body. The model is founded upon a hierarchy of sequence-dependent local energies that describe physically distinct interactions, involves only local parameters, can capture important local features that are below the resolution of other coarse-grained models, and can also capture important non-local features as have been observed in various investigations. A novelty of the model is its ability to account for the intrinsic, pre-existing stress in an oligomer. A complete parameter set for double-stranded, B-form DNA, in standard environmental conditions, has been estimated using an extensive database of atomic-resolution, explicit-solvent MD data produced by a consortium of groups. In this talk, an overview of the model and various mathematical issues associated with its parameterization will be discussed, as well as various examples illustrating some features and limitations of the model.

For any given oligomer, our model delivers an internal energy and a Gaussian probability density function on the associated internal configuration space, where the degrees of freedom are the relative displacement and rotation of each rigid base on each strand of the oligomer. The internal energy model is based on a hierarchy of sequence-dependent local energies that describe physically distinct interactions between various groups of proximal bases. Consistent with a nearest-neighbor assumption, we consider only the first two members of the hierarchy that describe the local interactions between the two bases in a monomer and the four bases in a dimer. Moreover, we characterize these interactions by a finite set of parameters that depend only on the local monomer and dimer sequence. The internal energy of an arbitrary oligomer of any length is then defined by a construction rule in which the local interaction energies are superimposed. We show that an internal energy constructed in this way provides a natural model for the intrinsic curvature and flexibility of an oligomer. Indeed, we show that these properties are determined by the local parameters in a non-trivial way through the construction rule. Moreover, our internal energy also provides a natural model for the intrinsic pre-existing stress in an oligomer. This stress arises from the fact that each base cannot simultaneously minimize all its local interactions and must instead find a compromise. As a consequence, our model predicts that the intrinsic or ground-state curvature of an oligomer depends non-locally on its sequence. That is, local mutations of the sequence produce non-local changes in shape. The description of such non-local behavior using only local parameters is unique to our model and is consistent with recent observations in the literature.

A complete parameter set for our model was estimated using a maximum relative entropy approach on the space of normalized probability density functions. Specifically, we sought to minimize an objective functional defined as the sum of Kullback-Leibler divergences between the model and observed probability density functions for each oligomer in the MD database. The numerical treatment of this problem was complicated by various constraints on the set of admissible parameters: some of the parameters are symmetric, positive-semi-definite matrices of different sizes, and various independent superpositions of these matrices must be positive-definite. Through a detailed study of this system of constraints and the construction rule for the internal energy and hence probability density function for an oligomer, we constructed an analytical characterization for an approximate minimizer of the Kullback-Leibler objective functional. Using an initial guess based on this characterization, we were able to successfully minimize the objective functional using a constrained gradient flow procedure and thereby obtain a best-fit parameter set for our model. Various predictions using this parameter set have been compared with existing data on B-form DNA, both experimental and simulated, and both sequence-averaged and sequence-specific. Our comparisons show that the model predictions are consistent with accepted properties of B-form DNA, and that the model can successfully predict properties such as the non-local effects of single nucleotide permutations and the non-local context effects of various structural degrees of freedom.

**Luis alejandro Mahecha,** Department of Physics, Universidad de los Andes, Bogotá, Colombia
Juan Manuel Pedraza, Department of Physics, Universidad de los Andes, Bogotá, Colombia

## Effects of noise gene expression on background and cooperator-defector fitness

The models of evolutionary dynamics are usually based in a fixedbackground fitness and, when they include cooperation, they include a fixed level of cooperation, which means that it is deterministic. However, in a biological system each individual is going to have different fitness and cooperate in different degrees due to phenotypic variability, even in isogenic populations.This is an effect of the gene expression noise. Expression noise affects the fitness of an organism when its fitness depends on the advantage of some phenotype that is generate by a gene or group of genes, and an increase in gene noise expression can lead to a decrement of the total fitness. Our stochastic simulations show that the fixation time is altered if the background fitness is a non-linear function of the gene expression. Including phenotypic variability in Moran processes allows a more realistic approach to the evolution of cooperation. Detailed simulations of competition populations of cooperators and defectors would allow characterization of the importance of phenotypic variability and its utility as an evolutionary strategy.

# Membrane bending is critical for the stability of voltage sensor segments in the membrane

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## ABSTRACT

The interaction between membrane proteins and the surrounding membrane is becoming increasingly appreciated for its role in regulating protein function, protein localization, and membrane morphology. In particular, recent studies have suggested that membrane deformation is needed to stably accommodate proteins harboring charged amino acids in their transmembrane (TM) region, since it is energetically prohibitive to bury charge in the hydrophobic core of the bilayer. Unfortunately, current computational methods are poorly equipped for describing such deformations, since atomistic simulations are often too short to observe large-scale membrane reorganization and most continuum approaches assume a flat membrane. Previously, we developed a method that overcomes these shortcomings by using elasticity theory to characterize equilibrium membrane distortions in the presence of a TM protein, while using traditional continuum electrostatic and nonpolar energy models to determine the energy of the protein in the membrane. Here, we linked the elastostatics, electrostatics and nonpolar numeric solvers to permit the calculation of energies for non-trivial membrane deformations. We then coupled this procedure to a robust search algorithm that identifies optimal membrane shapes for a TM protein of arbitrary chemical composition. This advance now permits us to explore a host of biological phenomena that were beyond the scope of our original method. We show that the energy required to embed charged residues in the membrane can be highly non-additive, and our model provides a simple mechanical explanation for this non-additivity. Our results also predict that isolated voltage sensor segments do not insert into rigid membranes, but membrane bending dramatically stabilizes these proteins in the bilayer despite their high charge content. Additionally, we use the model to explore hydrophobic mismatch with regard to nonpolar peptides and mechanosensitive channels. Our method is in quantitative agreement with molecular dynamics simulations at a tiny fraction of the computational cost.

**Matthew Graham**, University of Warwick, Coventry, UK
Thomas House, University of Warwick, Coventry, UK

## Dynamics of Stochastic Epidemics on Heterogeneous Networks - Variance of an epidemic during early growth period

Epidemic models currently play a central role in our attempts to understand and control infectious diseases. Here, we derive a model for the diffusion limit of stochastic susceptible-infectious-removed (SIR) epidemic dynamics on a heterogeneous network. Using this, we consider analytically the early asymptotic exponential growth phase of such epidemics, showing how the higher order moments of the network degree distribution enter into the stochastic behaviour of the epidemic. We find that the first three moments of the network degree distribution are needed to specify the variance in disease prevalence fully, meaning that the skewness of the degree distribution affects the variance of the prevalence of infection. We compare these asymptotic results to simulation and find a good agreement for city-sized populations.

**Bradford Greening**, Rutgers University, New Brunswick, NJ, USA
Nina Fefferman, Rutgers University, New Brunswick, NJ, USA

## Infectious Disease and Families: The effect of long-term social affiliations on the evolution of social complexity in the face of epidemics

Social interactions have long been understood to expose populations to risk from infectious disease. Previous studies have shown that populations displaying only selfish local behaviors, in the absence of disease, could have evolved complex, highly stable social organizations, and that long-term social affiliations such as family bonds can aid in the advancement of social complexity. However, as the amount of social interaction increases in the population, so too does the potential for disease burden. We examine the tradeoff to the social organization between maintaining long-term social interactions and the detriment posed by the increased risk of disease.

**Meredith L. Greer**, Bates College, Lewiston, ME, USA
Kathryn L. Cottingham, Dartmouth University, Hanover, NH, USA
Holly A. Ewing, Bates College, Lewiston, ME, USA
Kathleen C. Weathers, Cary Institute of Ecosystem Studies, Millbrook, NY, USA
Laura M. Griesinger, Bates College, Lewiston, ME, USA
Cristina M. Herren, Dartmouth University, Hanover, NH, USA
Sophie Leonard, Bates College, Lewiston, ME, USA
Audrew Lustig, Bates College, Lewiston, ME, USA and French Institute of Pondicherry, India

## Life cycle dynamics of *Gloeotrichia echinulata* and connections to nutrient cycling

*Gloeotrichia echinulata* is a large nitrogen-fixing cyanobacterium that has been identified in several northern New England lakes. We hypothesize that *G. echinulata* could accelerate eutrophication by contributing to increased quantities of nitrogen and phosphorus in the water column. Our group has collected data at Lake Sunapee, New Hampshire, USA, for several years. Differential equations and statistical approaches have been employed in conjunction with both weekly and daily data sets to help determine key drivers of the *G. echinulata* life cycle. Knowledge of this life cycle may bring better understanding of the role of *G. echinulata* in moving nutrients into the water column.

Our group has collected several years of weekly data, taken from multiple sites, on the recruitment rates of *G. echinulata*. Recruitment is a life cycle phase that follows shortly after the germination phase, when *G. echinulata* changes from dormant to active. During recruitment, *G. echinulata* moves from sediment to water column and can unlock phosphorus that has been trapped in the sediment. The literature suggests possible influences of light, temperature, and growing degree days on both the germination and recruitment stages in the life cycle of *G. echinulata.* We model these suggestions and compare their results with the weekly data.

Additionally, a researcher at one site has collected multiple years of daily data showing *G. echinulata* abundance in the water column. Modeling explores the relationship between current abundance and factors including recent abundance, light, and temperature. During its life cycle phases in the water column, *G. echinulata* can fix nitrogen from the air, thus introducing additional nitrogen to the water column.

Finally, we construct a coupled differential equation model of nitrogen (N) and phosphorus (P) cycling. The model gives a way to quantify the effects of *G. echinulata* on internal N and P loading, indicating the extent to which varying abundances of *G. echinulata* can shift equilibrium values of N and P.

**Frances Hall, Earlham College, Richmond, IN and NIMBioS: National Institute for Mathematical and Biological Synthesis, Knoxville, TN, USA**

**Jessica Welch, University of Tennessee and NIMBioS, Knoxville, TN, USA**

**Dawn Woodard, Appalachian State University, Boone, NC and NIMBioS, Knoxville, TN, USA**

Kimberly Gwinn, Department of Entomology and Plant Pathology, University of Tennessee and NIMBioS, Knoxville, TN, USA

Vladimir Protopopescu, Center for Engineering Science Advanced Research, Oak Ridge National Laboratory, Oak Ridge and NIMBioS, Knoxville, TN, USA

Dan Ryan, NIMBioS, Knoxville, TN, USA

## Harnessing the arsenal of nature: developing natural pesticides

Plants, insects and microorganisms ensure their survival by producing an arsenal of natural chemical weapons to escape herbivores, predators and competitors. Research in the laboratory of Dr. Kimberly D. Gwinn is aimed at achieving and maintaining the critical goal of sustainability by developing highly effective, environmentally friendly, low-toxicity bioactive natural products for food preservation and as viable alternatives to conventional chemical pesticides. In the 2012 REU, students will examine the effects of essential oils on spore germination and growth of a biological control fungus. The goal of this research is to develop predictive models for the development of 'stacked' natural control systems.

**This is an Undergraduate Poster

**Jason Hammond,** Applied Mathematics, University of Colorado, Boulder, CO, USA
David M. Bortz, Applied Mathematics, University of Colorado, Boulder, CO, USA

## Modeling and Simulation of Biofilm Fragmentation in Fluid Flow

In this talk we use the immersed boundary method to simulate the interaction of fluid flowing in a tube with an attached biofilm on the inner surface of the tube. We use the incompressible viscous Navier-Stokes (N-S) equations to describe the motion of the flowing fluid. In this simulation we can assign different density and viscosity values to the biofilm than that of the surrounding fluid. We look specifically at the adaptations in the simulation which arise as a result of a highly viscous biofilm compared to the surrounding fluid. Also included in this simulation are breakable linear springs connecting the particles in the biofilm which allow us to include biofilm fragmentation and detachment into the model. We discretize the fluid equations using finite differences and use a projection method with an iterative multigrid scheme to solve at each time step. Multigrid is used because the biofilm has a different density and viscosity than the surrounding fluid which causes the coefficients in the N-S equations to be non-constant in space and time. We apply this model in both two and three dimensions.

**Johanna Hansen**, Queen's University, Kingston, ON, Canada
Troy Day, Queen's University, Kingston, ON, Canada

## Coinfection, Competitive-Release and the Evolution of Resistance: A Mathematical Analysis

Experimental studies have shown that within-host competition between coinfecting strains can affect the growth and transmissibility of a strain. This in turn could have a serious effect on the emergence of resistant pathogens and their rate of spread through a population. However, when modeling the emergence and spread of drug resistance, the entanglement of coinfection has been mostly ignored.

We adapt the basic susceptible-infected model, to model the emergence of drug resistant pathogens under drug treatment pressure when there is coinfection. We are able to derive the invasion condition $R_0$ for a resistant pathogen under a coinfection framework thereby explicitly linking the emergence of drug resistance to the life history parameters of the pathogen and how they are affected through competition and drug action. This framework allows us to explore analytically the effect of competitive release on the emergence of resistant pathogens. We show that whether or not coinfection and competitive release promotes invasion depends on the relative values of the epidemiological parameters and thus the particular epidemiological cost associated with resistance.

Since we are also often interested in the growth of resistance once invasion has occurred we explore the rate of increase of resistance numerically. In addition, we can analytically estimate the growth of resistance when the coinfection efficiency is assumed to be small and determine whether coinfection will increase or decrease the rate of growth of resistance under this assumption.

We draw attention to the fact, that coinfection and competitive release play an important role in the emergence and growth of resistant pathogens. This phenomena could be a potential target to control drug resistance. By reducing the amount of competitive release or coinfection we could potentially have resistance emerge at a higher treatment rate, or grow at a slower rate. This could be achieved by potentially reducing the level of transmission, using drugs that target specific life stages where competitive release does not occur, or altering the dosage level of a drug.

**Niklas Hartung**, Aix-Marseille University, Marseille, France
Guillemette Chapuisat, Aix-Marseille University, Marseille, France
Florence Hubert, Aix-Marseille University, Marseille, France

## Metastatic growth in vivo and in silico

In this research project we want to study a tumour growth model adapted to the modelling of a targeted radiotherapy. This therapeutic approach, developed in particular in the TIRO research laboratory in Nice (France), consist of inducing a iode accumulation capacity in non-thyroidian cancer cells based on the gene expression of the Natrium iode symporter (NIS), thus facilitating the destruction of the tumour through a iode 131 radiotherapy. In preclinic models, the NIS transfer in cancerous cells can equally be used for the in vivo tracking of proliferating cancer cells and derived metastases.

Our aim is the development of a metastatic growth model distinguishing proliferating and quiescent cells. This model will be based on an ODE model established by Gyllenberg and Webb in 1989 which describes the primary tumour growth in terms of a dynamic exchange between proliferating and quiescent cell compartments, and on a size structured model initiated in 2000 by Iwata, Kawasaki and Shigesada describing metastatic growth. We will revisit the Gyllenberg-Webb model in view of its applicability in a preclinic context. Furthermore, a new metastatic growth model will be proposed. The parameter identifiability in these models will be treated.

Title: ***Myxococcus xanthus* Cluster Dynamics**

Authors: **Cameron Harvey**, Dale Kaiser, Amy Buchmann and Mark Alber

Abstract:
Many bacteria species can colonize surfaces by coordinating movement between individual cells. How cells coordinate such collective motion is an active area of study. *Myxococcus xanthus* is a common soil bacteria that is studied in part for the social coordination observed when cells are grown on different surfaces. Individual cells are flexible rods covered by a viscous polysaccharide capsule that creates an adhesive interaction between cells. *M. xanthus* cells regularly reverse direction of their motion and organize into single layers of small clusters and large rafts of cells at the edge of a spreading population. We describe in this talk simulations of the *M. xanthus* swarm using a Subcellular Element Model (SCE), developed and implemented by our group on a GPU computer cluster, to study how individual cell properties give rise to the clustering patterns seen in experimental movies. Coupled simulations and experimental bacteria tracking demonstrated how the flexibility, adhesion between cells and cell reversals impacted the dynamics of cell clusters resulting in better understanding of how these bacteria effectively colonize surfaces.

Erin Bodine, Rhodes College, Memphis, TN, USA
**Elysia Hassen**, Rhodes College, Memphis, TN, USA

## Comparing the Impact of imposing the Allee Effect on the Predator versus Prey Populations in a Discrete Time Model

The Allee effect is a biological phenomenon in which individuals in small populations experience lower reproductive and survival rates which diminish as the population becomes larger. Several models of predator-prey dynamics have been studied which introduce the Allee effect into the prey population. We propose a discrete-time model which incorporates the Allee effect into predator-prey dynamics by imposing the Allee effect on the predator population. We analyze the stability of equilibria and explore the system dynamics over a variety of parameter scenarios through numerical simulations. We then compare these results to an existing model of predator-prey dynamics where the Allee effect is imposed on the prey population.

**Alan Hastings**, University of California, Davis, CA USA

## Simple approaches to dealing with resource pulses: consequences for persistence and dynamics

Resource pulses have been found to play an important part in ecological dynamics. However, most current simple models in ecology do not include large temporal variation in resources. There are detailed models in ecology, such as those based on the dynamic energy budget (DEB) approach that have proved useful, but these are too complex to use in data poor situations and also do not provide general insights. In contrast I will develop simple models that incorporate the key ingredients of temporally varying resources and simple descriptions of age structure in consumers to show the importance of explicit inclusion of these two key ingredients in understanding persistence.

**Jane Heffernan**, York University, Toronto, Canada
Suma Ghosh, University of Utah, USA

**The effects of pre-existing immunity in seasonal influenza**

Seasonal influenza continues to cause waves of infection every year. Vaccination programs aid individuals and populations in resisting infection, however, the vaccine is usually imperfect and may not confer immunity against the strain in circulation. Immunity gained from infections or vaccines from previous years will aid an individual, and a population, in resisting infection through partial immunity. The extent of these effects however, on the individual and the population, have not been quantified. We have developed a model of seasonal H3N2 influenza infection including epidemic and inter-epidemic periods. The model includes the effects of partial immunity and vaccination and tracks two years of infection history. The model is used to compare and contrast the benefits of an imperfect vaccine and pre-existing immunity on an individual, and on a population. Latin hypercube sampling is employed to determine individual and population parameters which most affect the spread and impact of influenza infection.

**Randy Heiland**, Indiana University, Bloomington, IN, USA
Jamie Champlin, North High School, Columbus, IN, USA
Shinya Ito, Indiana University, Bloomington, IN, USA
Alan Litke, University of California, Santa Cruz, CA, USA
Andrew Lumsdaine, Indiana University, Bloomington, IN, USA
John Beggs, Indiana University, Bloomington, IN, USA

## Introduction to Modeling and Computational Neuroscience using Python

Neuroscience offers a rich domain of crosscutting sciences (e.g. biology, chemistry, physics) and therefore has the potential to be of interest to a wide variety of students. The subject of the [human] brain adds even more appeal due to its wondrous complexity and remarkable abilities, e.g. learning, memory, vision, consciousness – concepts that everyone can appreciate. Computational neuroscience brings in more core subject areas, primarily mathematics and computer science. It offers students an important hands-on experience, letting them apply concepts learned in their classrooms and, for some, challenging them to step outside their comfort zone into higher math and new programming languages.

As part of a NSF grant related to the analysis of causal connectivity of neurons, our university team has formed a collaboration with a high school physics teacher to share the excitement of neuroscience with high school students and, hopefully, establish a long term academic relationship that will help encourage students to major in science or mathematics in college. The first phase of this collaboration involved a presentation to four different physics classes (Honors or AP-level), consisting of about 100 students total, who ranged from freshmen to seniors. The presentation discussed computational science, in general: experiments, modeling, simulation, and analysis; but the focus was on computational neuroscience and the Python programming language. Many of the students were completing a unit on electronic circuits, so we demonstrated, using visually engaging simulations, how a neuron could be modeled as a simple (leaky integrate and fire (LIF)) R-C circuit and how this led to the important concept of a neuron spike. We then introduced the differential equation associated with the LIF model and the few lines of Python code that could numerically solve it. Following this simple, single neuron model, we discussed the historically significant Hodgkin-Huxley model (with its more complicated differential equation and electronic circuit). Lastly, we demonstrated the Izhikevich model, a pair of coupled differential equations, and how it was used to simulate a network of spiking neurons.

The presentation included many visuals related to the structure and function of neurons – axons, synapses, spiking behavior, and neuron networks. We also asked thought-provoking questions about memory, self-awareness, etc., as well as ethical questions related to animal testing. Somewhat related to this last topic, we also pointed out the availability of inexpensive do-it-yourself (DIY) neuroscience experiments that involve a cockroach leg.

This initial phase of our high school-university collaboration certainly had its challenges. Probably the most challenging was the mathematics (differential equations) since only about half of the students had taken calculus. But overall, we believe it was a very positive experience – for all of us. We asked the students to anonymously answer just two follow-up questions related to the presentation – what did they like best and what did they like least? We will present some simple statistics about these answers.

There are a number of directions our collaboration could take from this point: simple email exchanges or social networking groups, tours of university labs, or the formation of afterschool or weekend clubs, e.g. Python programming/simulations or DIY experiments using hardware. We are discussing the possibilities and we hope to learn lessons from other science educators.

Emily Rogers, College of Computing, Georgia Institute of Technology, Atlanta, GA 30332-0280, USA.
M. Shel Swenson, School of Mathematics, Georgia Institute of Technology, Atlanta, GA 30332-0160, USA.
**Christine E. Heitsch**, School of Mathematics, Georgia Institute of Technology, Atlanta, GA 30332-0160, USA.

## Introducing secondary structure profiling for small RNAs

The biomedical importance of small RNA molecules only continues to grow. Yet, even at this length scale, reliably predicting the native base pairings of an RNA sequence remains a significant open problem in computational molecular biology. We present a novel combinatorial method, RNA profiling, for identifying the most probable combinations of native base pairs across a Boltzmann ensemble of secondary structures. Proof-of-principle results show that profiling is straightforward, stable and surprisingly comprehensive for sequences on the order of 150 nt, which includes numerous classes of small RNA molecules.

# Mass action kinetics applied to ODE models of the pituitary-ovarian axis: Multiple stable periodic solutions simulate normal and acyclic clinical observations.

March 30, 2012

Mathematical models developed on clinical correlation and in-vitro causation were first applied to endocrine regulation of the pituitary-ovarian axis in women by Schlosser and Selgrade in 1999. The resulting model used biochemical properties of Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Estradiol (E2), Progesterone (P4) and Inhibin (INH) for stable, periodic in-silico representation . With successful parameter estimation the Schlosser/Selgrade models accurately reflected mean serum levels and oscillatory behavior as reported by McLachlan et al. (1990). Subsequent incarnations of Harris et al. (2000) and Pasteur (2011) merged the pituitary and ovarian sub-systems and expanded the model to represent both Inhibin A (INH-A) and Inhibin B (INH-B) respectively. Thorough analysis of these models revealed an additional stable periodic solution in the five-hormone model that resembles hormone levels of patients with Polycystic Ovarian Syndrome (PCOS). As PCOS is seen as primarily a hyper-androgenic disorder, the inclusion of Androgens into the Schlosser/Selgrade model seems necessary to produce accurate simulations of serum pituitary-ovarian hormones in women with PCOS. As Testosterone (T) is the dominant female androgen and is significantly increased in PCOS patients, we focus our efforts on modeling pituitary feedback and inter-ovarian follicular growth properties as functions of circulating free T levels reported by Sinha at al.. Structurally based on in-vitro findings of Yasin et al. and Weiss et al., parameters have been identified that simultaneously simulate LH, FSH, E2, P4, INH-A and INH-B of Welt et al. and free T levels of Sinha et al.. The resulting model expands that of Selgrade et al. to a system of sixteen ordinary differential equations that applies mass action kinetics to follicular phase growth. Bifurcation analysis reveals multiple periodic solutions that approximate clinical observations of circulating hormones in normal and PCOS patients with increased accuracy. The new model will allow investigators to study potential hormone interventions to return acyclic patients to regular ovulatory cycles.

## Modeling early evolution of human immunodeficiency virus

**Kelly Hennessey**, St. Olaf College, Northfield, MN, USA and NIMBioS: National Institute for Mathematical and Biological Synthesis, Knoxville, TN, USA
Vedaste Mutambuka, University of Arkansas, Little Rock, AR and NIMBioS, Knoxville, TN, USA
Anthony Rhoads, McKendree University, Lebanon, IL and NIMBioS, Knoxville, TN, USA
Vitaly Ganusov, Department of Microbiology, University of Tennessee and NIMBioS, Knoxville, TN, USA
Calistus Ngonghala, NIMBioS, Knoxville, TN, USA

HIV establishes a life-long chronic infection in vast majority of infected individuals despite strong antiviral responses elicited by the host. High mutation rate of HIV is thought to be one explanation for the ability of the virus to avoid host's immune response yet whether the observed rates of mutation are sufficient to explain rapid appearance of viral variants escaping recognition by T cell immunity is unclear. During this project we will formulate models of HIV evolution and investigate the role of mutation and recombination in early diversification of HIV in patients.

**This is an Undergraduate Poster

**Sarah Hews**, Hampshire College, Amherst, MA, USA

## Using biological research articles throughout the first-year mathematics curriculum

Using student-selected scientific research articles in the first year Calculus sequence allows for students to study cutting edge applications and enriches the class by bringing in a diverse set of examples. Students study topics that they are interested in and develop their own motivation for studying the mathematical concepts. The following topics will be discussed: the areas of study that are conducive to student-selected articles, how to assist students in picking topics and searching for articles at the right level, and how to craft appropriate assignments. Specific materials will be available including citations of articles that students have used, materials created to assist the students in understanding the graphs and equations in the articles, and assignments that have been reviewed positively by the students.

## Optimal Control on Polynomial Dynamical Systems Expedited by Use of Algebraic Geometry

Franziska Hinkelmann
Mathematical Biosciences Institute, The Ohio State University

Systems biology aims to explain how a biological system functions by investigating the interactions of its individual components from a systems perspective. Modeling is a vital tool as it helps to elucidate the underlying mechanisms of the system. My research is on methods for inference and analysis of polynomial dynamical systems (PDS). This is motivated by the fact that many discrete model types, e.g., Boolean networks or agent-based models, can be translated into the framework of PDS, that is, time- and state-discrete dynamical systems over a finite field where the transition function for each variable is given as a polynomial. This allows for using a range of theoretical and computational tools from computer algebra, which results in a powerful computational engine for model construction, parameter estimation, and analysis methods such as steady state behavior and optimal control.

**William Holmes,** University of British Columbia, Vancouver, BC, Canada

## Regulatory Control of Response Thresholds in Polarizing Cells

Chemotactic cells can be either sensitive or insensitive to noisy environments. Some require sufficiently large heterogeneous stimuli to respond, others undergo random motion in the absence of directed stimuli, and yet others transition between the two behaviours. Motivated by recent experimental work on GTPase polarization in HeLa cells, we investigate biochemical control of response thresholds that determine these phenotypes. A minimal model of GTPase / Phosphoinositide interactions, developed based on these experiments, is presented. Using a new nonlinear PDE bifurcation technique, we show the presence of both threshold and instability driven patterning, map the dependence of response thresholds on experimentally probed parameters, and discuss the biological implications of model – experiment agreement. Time permitting, we will discuss the more general mathematical and biological structure responsible for this threshold control which is not specific to the proposed biochemical network.

**Thomas House**, Mathematics Institute, University of Warwick, UK.

## Contagion in a Clustered Context

Mathematical models are now routinely used in infectious disease epidemiology to inform public health policy. One of the key features of the contacts that transmit most infectious diseases is transitivity: a lot of your contacts are each others' contacts, too. But modelling this feature is tricky because of the correlations that build up on the network of contacts.

This talk will report advances on three relatively recent approaches to this problem: First, specialisation of the network topology to a local-global system (or *hypergraph*); secondly, proposal of improved moment closure schemes; and thirdly methods based on non-independent Bernoulli trials that can also be adapted to behavioural / 'complex' contagion processes.

Biological insights gained include:

1. The role of different types of transitivity in slowing disease spread – i.e. does it matter if most of the triangles are in complete graphs of size four or above?
2. A counter-intuitive result about contact tracing / hyperparasitism.
3. Intuitions for why clustering enhances the spread of some complex contagions.

These will be discussed alongside the mathematical methodology.

**Dan Hrozencik**, Chicago State University, Chicago, IL, USA
Tim Comar, Benedictine University, Lisle, IL, USA

## Comparison of Boolean and Continuous Models for Gene Regulatory Networks

We compare Boolean and ordinary differential equations models for gene regulatory networks with three or four genes and up to five connections between the genes. We establish conditions for when the qualitative Boolean models and the quantitative ordinary differential equations models exhibit the same dynamical behavior.

Glenn Webb, Vanderbilt University, Nashville, TN, USA
**Xi Huo**, Vanderbilt University, Nashville, TN, USA

## An Age-dependent Population Model with Contact Tracing in Epidemic Diseases

Conatct tracing is an important method that has been used in the control of endemic contagious disease for decades, but we do not know much about the effectiveness or even the necessity of contact tracing yet. Contact tracing, followed by isolation, can reduce an additional number of infected individuals who are not removed by isolation process. That is the reason contact tracing is considered to be a useful method for reducing infections. Most of us believe that if some is good then more is better. So people intuitively deduce that high level contact tracing (those trace more contacts or last for longer period of time) results in having less infections than relatively low level contact tracing does. But that argument is not always the case according to our model.

We build a deterministic SIR model with isolation and contact tracing in the control of an epidemic disease. The model is applicable to diseases like smallpox, H1N1, SARS and some modern influenzas. We are able to conclude that tracing too many contacts during the contact tracing period might just postpone the outbreak of the disease and might NOT reduce infections effectively. Of course, it does not mean that we have the same kind of results for all infectious diseases and contact tracing strategies. There is a subtle connection between the apparence of the special case and the nature of the epidemic disease.

I will be interested in presenting some background of contact tracing, introducing the main model, demonstrating simulation results of different cases, explaining mathematically why the special cases appear and providing suggestions about how to choose a suitable contact tracing level. I'm also looking forward to knowing how well the model together with the conclusion and explanation can be understood by researchers from related areas, and any suggestions about either model improvement or future study will be appreciated very much.

## Qualitative simulation of the nonlinear dynamics of gene regulatory networks

We consider a specific class of ODEs well-accepted in the literature as adequate to model the essential features of the complex dynamics of Gene Regulatory Networks (GRN). In these models, the actions of transcriptional factors on genes depend on their concentration values, and can be modeled by either binary on-off or continuous steep sigmoidal functions around certain threshold concentrations. The network dynamics is modeled by either Boolean or piecewise linear equations in the former case, and by highly nonlinear equations in the latter one.

In a continuos framework, the mathematical problem related to such networks deals with the analysis of the behavior in narrow domains, called *switching domains*, where at least one variable is close to one of its thresholds. The current lack of precise and quantitative information on the biochemical reaction mechanisms underlying regulatory interactions, on kinetic parameters and threshold concentrations along with the size and interaction complexity of the GRNs makes, on the one hand, the solution of this problem particularly challenging, and, on the other hand, the design and implementation of an automated symbolic tool necessary. For piecewise linear models, with Heaviside dose-response functions, a computational analyzer, called GNA, of the qualitative dynamics of GRNs has been proposed (de Jong et al., 2004). The assumption GNA is based on considerably simplifies the analysis but it raises the problem to find a proper continuous solution across threshold hyperplanes. To this end, it adopts the Filippov approach that is not flawless when applied to approximate the limit solutions of a continuous model (Bacciotti, 2003).

In this talk, we consider models with sigmoidal response functions that vary continuously from zero to one with a steep rise around certain threshold concentrations. The ensuing dynamics is both linear and nonlinear with different time scales, and is analyzed with the singular perturbation method adapted to the considered class of models (Plahte and Kjøglum, 2005). The equations of motion for switching domains may raise several mathematical difficulties that lead to an heavy, or even intractable, computational problem. But, the biologically reasonable assumption that each transcriptional factor only regulates one gene at each of its threshold simplifies the problem and allows us to establish sound rules, computationally tractable, that determine the calculation of trajectories as the sequence of phase space domains through which the system passes. When suitable conditions are fulfilled (Ironi et al.,2011), the simulation outcomes do capture the network dynamical properties dependent on the model structure and invariant for ranges of model parameter values. The proposed algorithm has been designed for GRNs but is applicable to study the multi-scale dynamics of threshold-dependent regulatory systems from other application contexts that may be reasonably modeled by the class of ODE models and assumptions we consider.

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## Effect of functional form of interaction on evolution of cooperation

Intraspecific cooperative interactions are widely observed in various taxonomic groups. Evolutionary processes of cooperative level have been well studied by using adaptive dynamics. Those studies generally assumed that a consequence of cooperation is a function of total investment from interacting players. However, an alternative functional form may be possible depending on substantial relationship among players. For example, the consequence can be summation or products of functions of each individual investment. We investigate the effect of functional form of interaction on evolution of cooperation.

In the analysis, we consider that $n$ individuals interact each other in a local habitat, where $i$-th individual invest $x_i$ resources for cooperation. The individual investment for cooperation linearly decreases its basal fitness. However, the cooperative investments within the habitat contribute to increase fitness of habitat members. We consider three types of fitness enhancement (benefit) functions, *i.e.* an additive investment ($B(\Sigma x_i)$), an additive effect ($\Sigma B(x_i)$) and a multiplicative effect ($\Pi B(x_i)$).

According to analysis of evolutionary dynamics, we found that evolutionary consequence depends on the functional forms of benefit. In the additive investment and additive effect cases, cooperative level always becomes monomorphic. In the multiplicative effect case, evolution can result in dimorphism in dependence on the functional form of $B(.)$, but never achieve polymorphism with more than two cooperative levels. When the assumption of linear cost is relaxed, it influences the result of additive investment case only, where polymorphism of cooperative level is possible.

Our analysis indicates that the functional form of interaction is an important determinant of evolutionary dynamics of cooperation.

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## A Host-Vector Model for Citrus Greening with Roguing: Persistence, Transients and Other Behavior

Citrus greening, a bacterial infection of citrus trees, has had a severe impact on the citrus industry of Florida since its first detection in 2005. A recent study estimates that the disease has caused over $3 billion in lost revenue and over 6,000 lost jobs in the state. Citrus greening is also present in Georgia, South Carolina and Louisiana. More significantly, in January 2012 the Texas Department of Agriculture and the USDA confirmed the presence of the disease in Texas, and on March 30, 2012 a grove in California was determined to be positive for citrus greening. Together the industries in Florida, California and Texas comprise about 98% of the citrus production of the United States.

Citrus greening has been impossible to eradicate and very difficult to control. The disease exhibits a latent period which has been observed to last anywhere from 6 months to 6 years. During this time the tree is asymptomatic but can be infectious. The vector for citrus greening is the Asian citrus psyllid; transmission occurs during feeding in the nymphal and adult stages. The psyllids were first discovered in Florida in 2000 and are now well distributed throughout the citrus-growing areas of the state. In addition to those states with citrus greening, Arizona, Hawaii, Mississippi and Alabama are now also home to the insect. Various management methods, with none being overly successful, have been attempted to control the disease. Citrus growers are currently implementing a rogue and replant strategy where infected trees are removed and replaced with new trees. Often, replanted trees quickly become infected; there is the possibility that the soil acts as a reservoir for the disease.

Previously, we developed a model for the population dynamics of citrus greening at the grove-scale, explicitly including both the tree and vector populations. The tree population is divided into susceptible, infectious and asymptomatic, infectious and symptomatic, and removed (considered to be dead) compartments. Roguing of symptomatic and dead trees occurs with a positive probability of the replanted tree directly entering the infectious state. Prior work also included calculation of the basic reproduction number, $R_0$, and determining a condition for the existence of an endemic equilibrium.

Here we perform further analysis on the model. The relation of $R_0$ to the extinction and persistence of the disease is discussed. Simulations suggesting additional stability behavior of the endemic equilibrium are included. By allowing for distinct roguing rates of symptomatic and dead trees we determine the effect of roguing strategy on $R_0$, the transient behavior of the disease, and the equilibrium level of susceptible (productive) trees. Finally we make a biologically relevant modification to the model which yields more complicated dynamics. The existence of two endemic equilibria becomes possible; conditions for such existence are discussed and numerical simulations are shown which indicate further stability results.

**Henriette Jager, Oak Ridge National Laboratory, Oak Ridge, TN, USA**

## Thinking Outside the Channel to Design Optimal Flow Regimes that Favor Salmon Populations and Energy Production

River flow influences salmon indirectly, through its effects on temperature, prey, refuge, and other direct influences on survival and reproduction. Recent studies suggest that slow, shallow habitat provides essential habitat for juvenile fishes, including Chinook salmon. In this study, I developed a quantile recruitment model for fall Chinook salmon that represents benefits of floodplain inundation on prey, salmon bioenergetics, survival, and recruitment. Cohorts of salmon from nests constructed in the same space-time quantile are tracked by the model until they exit the tributary. Using this simplified quantile model, I used a genetic algorithm to allocate a parametric function describing two pulse flows, where the magnitude, timing, and duration of seasonal pulse flows maximize salmon production and energy from hydropower. Multiple seeds were compared to ensure convergence among solutions beginning at different places in parameters space.

Results highlighted the importance of indirect effects of flow, mediated by temperature and access to productive floodplain habitat during late winter and early spring. The optimization recommended earlier peak flows and an alternative tactic for successful salmon production in warm climates. Peak flows tended to be steep and of shorter duration during drier hydrologic years and broader during wet years when shaped to maximize Chinook salmon production. These results will be compared with those of optimizations to maximize energy value for producers to determine the degree to which economic and salmon objectives are aligned at a seasonal scale.

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## Effects of Tachykinin Receptor Activation on Prefrontal Cortex Neuronal Activity

Tachykinins are neuromodulatory peptides found in the mammalian brain and high levels of tachykinin receptors are expressed on pyramidal neurons of the prefrontal cortex (PFC). The present study used the whole cell patch clamp technique and a mathematical model to investigate the ionic mechanisms underlying the responses of guinea pig PFC neurons to senktide, a tachykinin receptor agonist. Senktide (500nM) depolarized neurons, and at -70 mV in voltage-clamp, induced an inward shift of the holding current, a change that was accompanied by a decrease in membrane conductance. Current-voltage (IV) relationships showed that the senktide-sensitive current reversed at -91.6 mV, very near the calculated potassium equilibrium potential ($E_K$) of -93 mV. Elevations of extracellular potassium shifted this reversal potential in accordance with the Nernst equation. The response to senktide was similar to the response seen with extracellular cesium (5mM) or barium (200μM), known inhibitors of the inward rectifier potassium current ($I_{Kir}$). Simulations using a biophysically-based neuronal model consisting of twelve differential equations showed that decreased $I_{Kir}$ conductance yielded responses consistent with our biological data. We thus conclude that tachykinin receptor activation on PFC neurons may result in inhibition of the potassium current, $I_{Kir}$.

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## Theoretical Study of Algal Bloom Dynamics with Akinete Formation and Germination

The aim of this study is to investigate the population dynamics of harmful algal bloom by using the Joehnk's model with some generalizations. The present mathematical model is a second-order nonlinear nonautonomous system based on delay differential equations. One variable is the biovolume of vegetative cells and the other one is the number of units of akinetes. The akinete is a thick-walled dormant cell derived from a vegetative cell and it is considered as a potential and significant factor triggering the algal bloom. The formation and germination of akinetes are modeled with time delays, and the coefficients in the model are described by piecewise continuous functions in time. The time delay related to the carrying capacity is considered in the form of the Hutchinson's equation. The analysis is divided into two parts. In the first part, we investigate the local and global stability of an approximated autonomous system. In the second part, we discuss the numerical solutions of the original nonautonomous system for various simulation conditions.

In the first part, the local stability at critical point is analyzed for an approximated autonomous system derived from averaging the time-varying periodic coefficients. The Jacobian matrix obtained from the linearization near the critical points shows that one critical point at the origin is a saddle point. In the first quadrant where both populations are positive, the saddle point plays a role of unstable node because the eigenvector corresponding to the negative eigenvalue lies in the second and the fourth quadrant in the phase plane. The other critical point located in the first quadrant is an asymptotically stable node. There is no periodic solution in the autonomous system. By calculating the trajectories for various initial conditions and constructing a Lyapunov function, the asymptotically stable node is identified by a globally asymptotically stable node in the first quadrant. Nullclines, critical points and direction fields of the present system are compared with the similar but different autonomous systems such the prey-predator model and the Lotka-Volterra competition model.

Since the original nonautonomous system is highly complicated for mathematical analysis, in the second part, we performed the numerical simulation by solving the delay differential equations with the use of Runge-Kutta algorithm. From the simulated results in cases of virtual environments, we observed the following properties of the model: (i) the initial populations of vegetative cells and akinetes have no influence on the stationary periodic solutions, (ii) temperature variations are closely related to the population dynamics of vegetative cells and akinetes, especially to the number of blooming peaks, (iii) time delays related to the germination and formation of akinetes were negligible in population dynamics whereas the time delay related to the carrying capacity is strongly influential to the populations of vegetative cells and akinetes as well as the occurrence of an additional blooming peak.

## Boundary formation in developing tissues – a mathematical model for inter-cellular inductive Notch signaling

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In developing tissues, when cells expressing two different factors are juxtaposed under specific conditions, they give rise to a boundary of specialized cells. This phenomenon has been identified at the dorsoventral cell boundary during the development of drosophila wing disc, at the Apical Ectodermal Ridge (AER) of the vertebrate limb, and at the boundary between neural and non-neural ectoderm in neural crest formation. Specialized cells form at the boundary of Fringe expressing and Fringe non-expressing cells by a specific type of Serrate→Notch / Delta→Notch interaction, called as inductive signaling. The presence of Fringe is said to inhibit the binding ability of Serrate ligand to Notch and enhance that of Delta to Notch. Although several of the signaling elements have been identified experimentally, it remains unclear how the inter-cellular interactions can give rise to such a boundary of specialized cells. Here we present a simple ordinary differential equation (ODE) model involving Delta→Notch and Serrate→Notch interactions between juxtaposed Fringe expressing and Fringe non-expressing cells. When this ODE model is incorporated into a 2D spatial arrangement of cells using cell-based modeling environment – Compucell3D and SBML based ODE solver called Bionet solver, it shows that a boundary of specialized cells forms which expresses a higher level of Notch than the others. We analyze this model both analytically and numerically showing the conditions under which such a boundary is formed as observed in living systems. In addition, we also incorporate this model into a 3D cellular arrangement and show the formation of Apical Ectodermal Ridge in vertebrate limb.

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## Modeling stabilizing selection: expanding the OrnsteinUhlenbeck model of adaptive evolution

Comparative methods used to study patterns of evolutionary change in a continuous trait on a phylogeny range from Brownian motion processes to models where the trait is assumed to evolve according to an OrnsteinUhlenbeck (OU) process. Although these models have proved useful in a variety of contexts, they still do not cover all the scenarios biologists want to examine. For models based on the OU process, model complexity is restricted in current implementations by assuming that the rate of stochastic motion and the strength of selection do not vary among selective regimes. Here, we expand the OU model of adaptive evolution to include models that variously relax the assumption of a constant rate and strength of selection. In its most general form, the methods described here can assign each selective regime a separate trait optimum, a rate of stochastic motion parameter, and a parameter for the strength of selection. We use simulations to show that our models can detect meaningful differences in the evolutionary process, especially with larger sample sizes. We also illustrate our method using an empirical example of genome size evolution within a large flowering plant clade.

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## Sprouting Angiogenesis: An Integrated Experimental and Multiscale Modeling Study

Angiogenesis requires a highly coordinated cellular response to both cellular and molecular signals. This response is triggered by cell surface receptors responsible for the activation of an intracellular cascade that efficiently initiates migration and proliferation programs. While the molecular players that coordinate these effects have been identified, recent findings have expanded our understanding of cell-cell and cell-matrix interactions, affects endothelial cell responses to growth factors. Experiments have revealed that the cellular composition of a growing vascular sprout is molecularly and functionally heterogeneous. The endothelial cells at the invasive front exhibit unique properties and can be distinguished from their neighbors by the expression of a specific subset of molecules. Differentiating into tip, stalk, and phalanx cell types, the endothelial cells organize into sprouts, which branch and fuse to form networks that support blood-flow. Retinal angiogenesis in embryonic mouse provides an excellent experimental system to study all these aspects of angiogenesis.

Based on experimental data from retinal angiogenesis, we have developed a cell-based, multiscale mathematical model of sprout formation. The model incorporates three level descriptions: 1) VEGF activated Dll4-Notch signaling, which regulates endothelial differentiation; 2) tip, stalk and phalanx cell types for endothelial cells along the sprout; and 3) tissue level extracellular-matrix representation and dynamics of VEGF and other growth factors. The model reproduces many phenomena observed in sprouting angiogenesis, including sprout morphology dynamics and tip competition. Our simulations explain and predict some perturbation experiments on Notch/Delta and VEGF pathways.

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## Discriminating between models of neutrophil polarity through cell severing and perturbations of cell geometry

Many eukaryotic cells polarize and migrate, either spontaneously, or in response to external chemoattractant. Polarity is characterized by a rapid conversion from a round to an elongated morphology, with a leading lamellipod at the front. A widespread assumption is that the leading edge prevents formation of multiple fronts by generating long-range diffusible inhibitors or by sequestering essential polarity components. Experiments with tethered neutrophil-like cell line show that even cells with drastically altered "dumbbell" geometries still establish a unique front. Severing experiments, where a cell fragment is able to form a new axis of polarity, indicate that there is long range communication between the front and back of the cell that prevents the formation of multiple fronts.

However, we show that when cell geometry is altered, several proposed classes of reaction-diffusion (RD) models for polarity establishment either give rise to multiple fronts or are not able to re-animate upon severing. This allows us to show that proposed diffusion-based mechanisms are not sufficient for long-range inhibition by the pseudopod. We find that membrane tension doubles during leading-edge protrusion, and increasing tension is sufficient for long-range inhibition of multiple fronts. Furthermore, reducing membrane tension causes multiple pseudopods. We suggest that tension, rather than diffusible molecules generated or sequestered at the leading edge, is the dominant source of long-range inhibition that constrains the spread of the existing front and prevents the formation of secondary fronts.

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## Mathematical Modelling of Mutation Initiation and Acquisition in Stem Cell Driven Cancers

Most tissues consist of three classes of cells: stem cells, transit-amplifying progenitor cells, and differentiated cells. Many tumors also have a hierarchical organization, with the bulk of the tumor composed of relatively differentiated short-lived cells with a limited replicative potential. Tumors are thought to be maintained by a small subpopulation of cancer stem cells (CSC), which have the capacity to proliferate indefinitely, and drive tumor growth. It is unclear whether CSCs originate from stem cells or from de-differentiated mature cells. We consider a hybrid stochastic deterministic model of mutation acquisition in stem cells and their progeny. We study the effects of competition between cells both at the stem cell level (in a stochastic model) and the progenitor level (in an age structured PDE model), as well as the effects of de-differentiation of progenitor cells to stem-cell like state. We give estimates on the necessary division and mutation rates to maintain a stable cohort of mutant transit-amplifying cells due to progenitor mutations alone. However, to obtain unlimited growth, de-differentiation from progenitor to stem cell state is essential. Interestingly, effects of de-differentiation only become important once homeostasis, which limits the number of cells in the stem cell pool, is lost.

**Title**: Treatment for the Human Immunodeficiency Virus (HIV) using Highly Active Antiretroviral Therapy

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**Abstract**: We will present our work on treatment for the Human immunodeficiency virus (HIV) using Highly active antiretroviral therapy (HAART). We will use a system of ordinary differential equations (ODEs) describing the interaction of the HIV virus with the human immune system with two different classes of drugs representing a typical HAART treatment. Our goal is to maximize the CD4+ T-cells count in a patient while minimizing hazardous side effects of the drug treatment. We will derive optimality system and solve it numerically using a Runge-Kutta method.

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## Mechanisms for Coexistence in Host-Phage Systems with Nested Interaction Networks

Viruses are ubiquitous in nature and the most abundant biological life-form on Earth. Globally, their estimated abundance is $10^{30}$ particles. Viruses have profound ecological effects; by infecting, exploiting and sometimes killing their hosts, they affect the dynamics and composition of all types of biological communities. They are particularly relevant in the study of aquatic bacterial communities where they are thought to be responsible for 20-40% of bacterial mortality. In these communities different host species and their viral pathogens (i.e. phages) coexist, creating complex interaction networks where different viral strains have overlapping host ranges. A recent meta analysis of host-phage interaction networks revealed that such networks tend to be nested [1]. In nested systems, there is a hierarchy for who can infect whom. In particular, the specialist virus can infect the most permissive host, whereas the host that is most difficult to infect gets infected by the more generalist virus. The mechanisms through which viral strains with overlapping host ranges coexist are not well understood. For example, the emergence of nestedness may reflect important ecological principles at work that have been overlooked in the past where viral strains were often assumed to only infect a single host. In this study we ask if the property of nestedness might yield insight into mechanisms allowing coexistence in multi-strain host-phage systems.

We present our analysis of a multi-stain host-phage system using a modified Lotka-Volterra (LV) framework. LV models have been used in the study of phage-host interactions[2,3]. Here, we modify the typical LV framework to explicitly incorporate the interaction among N viral strains and N host strains. We begin by assuming that the N-by-N interaction matrix is perfectly nested. We solve the model for conditions of coexistence at equilibrium and assess the possibility of coexistence for systems starting away from equilibrium by looking at the stability of the boundary equilibria. We validate our results using numerical simulations and show how coexistence can be obtained via different types of dynamics which can be different from a locally stable steady state.

We find two general requirements for the coexistence of viral and host strains in perfectly nested systems. First, there should exist a trade-off in the viral strains between life-history traits and host range. These viral traits include: adsorption rate, burst size, and death rate. Second, there should exist a trade-off in the host strains between immunity and growth rate. We find that properties of these trade-offs can predict relative densities of the viral and host strains. Importantly, we find that the strength of the trade-off, as measured by its curvature in terms of species rank, determines the relative densities of viruses and hosts. For example, specialist viruses may have higher abundances than generalist viruses, or vice versa, depending on the relationship between life history traits and host range. We also study systems that are not perfectly nested. In these systems, we find that species can coexist if the viral host ranges are sufficiently different (specifically, if the interaction matrix is invertible). For non-invertible interaction matrices (e.g. complete overlap in host range) coexistence can still be achieved by quantitative changes in the strength of the interactions. Finally, we discuss how our analysis provide insights in the more general endeavor of understanding the relationship between the structure of networks and the properties of ecological communities such as biodiversity and stability. Specifically, we show that it is important to consider the constraints that the structure of interaction networks imposes on the different interaction parameters.

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## Crowdsourcing Curriculum Development in Mathematical Biology Education

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Crowdsourcing has been deployed to address a number of difficult problems. By stating open problems in a well--posed, succinct way and inviting the submission of pragmatic solutions to their solution, participation of individuals and groups that are not usually included is invited. By its very nature, mathematical biology education requires the participation of individuals that have frequently been isolated in academic disciplinary silos. Recent successes in open, interdisciplinary, research--rich undergraduate science education (see special issues of CBE Life Science Education (<http://lifescied.org/content/9/3.toc>) and Mathematical Modelling of Natural Phenomena (http://www.mmnp-- journal.org/action/displayIssue?jid=MNP&volumeId=6&seriesId=0&issueId=06>) have demonstrated the profit of collaborative interdisciplinary teams. Yet most curriculum development is by individual educators for their own classrooms and is not built upon adopting, adapting, and implementing vetted alternatives from colleagues and published literature. How do we prepare our students for the challenges of 21st century science, productive careers, and responsible citizenship? In an era of terabytes to petabytes of data amassed per day, of a globally interconnected communication network, electronically accessible open access journals, massively parallel computational power, personal real--time data acquisition devices, national collaboratories that make high--end instrumentation more accessible to wider communities, potential for personal fabrication, community sensor networks, and new modes of intellectual property such as Creative Commons, copyleft, wikis, blogs, re--mixes, and mash--ups, how are traditional expectations of students inappropriate? If we adopt a Citizen Science approach that would include students, teaching assistants, lab technicians who prepare lab course materials, novice and experienced faculty from biology, mathematics, and associated disciplines such as biological engineering and environmental studies, science and mathematics education researchers, quantitative and qualitative ethnographic evaluators, historians--philosophers-- sociologists--anthropologists of science and mathematics, and industrial employees who hire our students to do mathematical biology, I believe that we have the potential to not only address some serious challenges to our current practices, but also to serve as a pragmatic successful model for others to emulate.

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## Boolean vs. ODE models of gene regulatory and other systems

Many biological networks exhibit switch-like behavior. Examples include gene regulatory networks and neuronal networks. Boolean and other discrete dynamical systems with a finite state space appear to provide natural frameworks for modeling such systems. The dynamics of these models are often easier to study than the dynamics of ODE systems that incorporate more biologically realistic details, and the former models can be considered coarse-grained approximations of the latter. The question arises, however, under which conditions the dynamics of the Boolean approximations reliably reflect the dynamics of the underlying ODE systems.

In this talk we will define precise notions of correspondence between an ODE system and its Boolean approximations and review some results from the literature that prove correspondences for certain systems. Examples include models of gene regulation, neuronal networks, and classes of toy models that allow elucidation of some important mechanisms. This brief review will show some commonalities and differences between the results for the various classes of models.

We will then present some results on how these differences can be explained. Our particular focus will be the role of separation of time scales. While the results on neuronal networks and certain toy models hold as long as the separation of time scales is sufficiently large, the correspondence is lost in models of gene regulatory networks when the separation increases beyond a certain value. We will discuss which features of the underlying ODE's may explain this phenomenon.

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## Numerical Simulation of Blood-Wall and Blood-Plaque Interaction in Stenosed Artery Using FSI Modelling

Diseased arteries can create high levels of turbulence, head loss, and a choked-flow condition in which tubes can collapse. Most of these diseases are highly focal and must be caused by a local factor acting at a specific site. The stress and mass transfer at the blood-wall interface are important hemodynamic factors that influence biological responses. The formation of a stenosis is the most dire biological response. Hence, complete understanding of the relationship between pressure, flow, and symptoms for cardiovascular stenoses is a highly critical problem.

We want to describe the velocity field and the pressure inside a section of the aorta according to the nature of the arterial layers and the geometry. A problem of this type can be solved using Navier-Stokes equations for the fluid (blood) in an Arbitrary Lagrangian Eulerian framework (ALE). Furthermore we are interested in the dynamic analysis of the aorta.

Many models have been developed based primarily on fluid mechanics under the assumption of rigid wall were allowed to determine the flow characteristics such as recirculation zones and disruption of the flow. The majority of this work focusing on the study of the velocity field did not study the behavior of the wall vessel towards the fluid. There are several difficulties when studying the biomechanics of this structure : the three constituent layers of the tissue (intima, media and adventitia), the variability of the geometry of the arterial wall and their strong interaction with blood flow.

The aim of this work is to study, on one hand the fluid-structure interaction (FSI) between blood and atherosclerotic plaque and on the other hand, the interaction between blood and the arterial wall, in a 2D geometry using a FSI model. The atheroma plaque is composed of a lipid pool covered with a fibrous cap and both are modeled as hyperelastic materials, linear isotropic and elastic material properties are assumed for the vessel wall layers and the blood is supposed to be Newtonian. The parameters used in our simulations are taken from experimental data. We investigate the vessel wall mechanics effects on the recirculations downstream of the atheroma plaque and on the stress over the plaque in different degrees of stenoses.

**Damian Kajunguri**, SACEMA, University of Stellenbosch, South Africa
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## Cost-effectiveness analysis of tsetse and *Trypanosoma brucei rhodesiense* control through application of insecticides on cattle

The control of African trypanosomiasis or sleeping sickness by using trypanocidal drugs has been frustrated by drug resistance in addition to being expensive for most people in sub-Saharan Africa. Hence, the need to control the disease by attacking its insect vectors, the tsetse flies (*Glossina ssp*) which can be done by the farmers themselves.

We present a mathematical model for the transmission of *Trypanosoma brucei rhodesiense*, the acute form of trypanosomiasis in a multi-host and tsetse vector populations. To control tsetse and *T. b. rhodesiense*, a proportion, $p$, of cattle, one of the hosts considered in the model is taken to be kept on treatment with insecticides. Two strategies of cattle treatment are considered, that is, "whole-body" treatment of cattle with insecticides and "restricted application" of insecticides on cattle. An analytical expression of the basic reproduction number, $R_{0n}$, of the multi-host model is obtained and shown to increase with the number of hosts. For numerical analysis, the model is reduced to three hosts, that is, cattle, humans and wildlife, since cattle and wildlife are known to be the most *T. b. rhodesiense* reservoirs in sub-Saharan Africa. The basic reproduction number, $R_{03}$, of the three-host model is analysed to find the proportion of cattle needed to be treated with insecticides in each of the two strategies so that $R_{03} < 1$. Sensitivity analysis shows that $R_{03}$ is more sensitive to the tsetse natural mortality rate parameter. Numerical simulations are carried out to investigate the impact of treating cattle with insecticides on the tsetse population and incidence of *T. b. rhodesiense* in humans and the associated cost-effectiveness ratio per DALY averted is obtained. Results show that the control of tsetse vectors through restricted application of insecticides on cattle is more cost-effective in reducing the tsetse population and incidence of *T. b. rhodesiense* in humans compared to the whole-body treatment of cattle with insecticides. The results show the importance of restricted application of insecticides on cattle, a cheap, safe and farmer based strategy towards the control of tsetse and *T. b. rhodesiense*.

**Andrew Kanarek**, National Institute for Mathematical and Biological Synthesis, University of Tennessee, Knoxville, TN, USA

**Individual-based modeling and the consequences of Allee effects**

One of the advantages of using an individual-based modeling approach in ecology is to better understand the link between intra-specific interactions and population-level dynamics. In this case, certain assumptions about spatially localized behavior can influence how individual processes scale to higher levels of organization. Specifically, when individual fitness depends on the presence of conspecifics (i.e., density dependence), properties of local interaction neighborhoods and propensity for dispersal can have ecological and evolutionary consequences. Here I will focus on the scenario of a founder population at low density, and consider how positive density dependence (i.e., Allee effects) and spatial structure interact to impact population persistence. The overall aim is to highlight the spectrum of behaviors that emerge from our individual-based model in order to further consider approaches to approximate the results with aggregate models.

# Competition driven cancer immunoediting

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Abstract:

It is a well-established fact that in an actively proliferating state tumors up-regulate glucose consumption to meet increasing energy demands by switching to glycolysis. What is often neglected is that actively proliferating cells of the immune system also switch to glycolysis and thus also have increased energy demands. Moreover, while cancer cells can revert back to aerobic metabolism, rapidly proliferating cytotoxic lymphocytes are incapable for performing their function when adequate resources are lacking. Consequently, in the tumor microenvironment there must exist competition for the common resources between cancer cells and the cells of the immune system, which may drive a lot of the tumor-immune dynamics. In this paper we formulate a model of tumor-immune-glucose interactions as a predator-prey-common resource type system and investigate possible dynamical behaviors that may arise depending on intrinsic parameter values and the initial state of the system, including tumor elimination, tumor dormancy and unrestrained tumor growth. We propose that competition for common resources can be a possible mechanism that underlies the phenomenon of immunoediting, i.e., tumor elimination, equilibrium and escape.

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## Flux: A new building block for ecological networks

Ecosystems are often modeled using weighted digraphs, representing flow of energy or nutrients among compartments. Depending on the model, what a compartment represents may range from dissolved organic matter in a lake, to species with common properties living in a specific area. Flows among compartments may represent predation, uptake, excretion, etc.

Ecological Network Analysis (ENA) enables quantitative study of ecosystem models by formulating system-wide organizational properties, such as how much nutrient cycling occurs within the system, or how beneficial a particular species is to the entire ecosystem (keystone species). Most such properties are defined based on the digraph structure, the flow quantities associated with each edge, and storage values associated with each compartment (node).

While ecosystems seem to be made up of flows among compartments, neither flows, nor compartments can function by themselves. Motivated by Flux balance analysis (FBA, Kauffman, 2003) and metabolic control analysis (MCA), we propose a new building block for ecosystems, called fluxes. A flux is a subnetwork which represent the smallest process within the ecosystem that can theoretically sustain itself. This can be a material cycle within the ecosystem, or a simple food chain in a complex foodweb. Fluxes have interesting properties that render them extremely useful for ecological studies. For example, any ecological network has a unique set of fluxes. And any ecosystem model, steady-state or dynamic, can be expressed as a linear combination of its fluxes.

Identifying important fluxes for an ecosystem model might be as important as identifying important compartments (e.g., keystone species) or important flows (e.g., betweenness measure). We will focus on several quantitative ecosystem properties, and study how they are represented over fluxes. For example, the amount of material cycling that occurs within the whole ecosystem equals the sum of material cycling that occurs within each of its fluxes. This result holds regardless of the size or complexity of the model. We anticipate that other system-wide ecosystem properties are conserved by this decomposition. Finally, we will demonstrate an online tool that computes fluxes for any ecological network model (EcoNet: http://eco.engr.uga.edu).

**Michael Kelly**, University of Tennessee, Knoxville, TN, USA
Suzanne Lenhart, University of Tennessee, Knoxville, TN, USA

## The impact of spatial arrangements on intervention strategies in epidemic models

The role of spatial arrangements in a metapopulation on the spread and optimal intervention strategies of a cholera epidemic is investigated. We consider how the movement of individuals and water affects the optimal vaccination strategy. For each metapopulation, the model has an SIR system of differential equations coupled with an equation modeling the concentration of Vibrio cholerae in an aquatic reservoir. The model will be used to compare two basic spatial arrangements. The work is motivated by the recent cholera outbreak in Haiti and is in collaboration with Joseph Tien, Suzanne Lenhart, and Marisa Eisenberg.

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## Collective Behavior of Brain Tumor Cells: the Role of Hypoxia

We consider emergent collective behavior of a multicellular biological system. Specifically we investigate the role of hypoxia (lack of oxygen) in migration of brain tumor cells [1]. We performed two series of cell migration experiments. The first set of experiments was performed in a typical wound healing geometry: cells were placed on a substrate, and a scratch was done. In the second set of experiments, cell migration away from a tumor spheroid was investigated. Experiments show a controversy: cells under normal and hypoxic conditions have migrated the same distance in the “spheroid” experiment, while in the “scratch” experiment cells under normal conditions migrated much faster than under hypoxic conditions. To explain this paradox, we formulate a discrete stochastic model for cell dynamics [1,2]. The theoretical model explains our experimental observations and suggests that hypoxia decreases both the motility of cells and the strength of cell-cell adhesion. The theoretical predictions were further verified in independent experiments [1].

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# A Mathematical Model for Cell Membrane Deformation

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## Abstract

We present a simplified model of biological cells including a first layer, corresponding to the membrane and the actin cortex and a second one, representing the cell cytoplasm. The membrane-actin set is governed by Navier equations while the cytoplasm is assimilated to a viscous fluid, described by the Navier-Stokes system. At the inner boundary, between the cortex and the cytoplasm, we match the velocity displacement with the fluid velocity. The membrane, which faces the extracellular medium, is free to move. To take into account the deformation of the initial configuration, we use the Arbitrary Lagrangian Eulerian method to develop a fluid-structure interaction model for the mesh displacement. Simulations showing the emergence of filopodium, a typical structure in cells undergoing deformation, are presented.

Keywords: Mathematical modeling, cell membrane, fluid-structure interaction, numerical simulations.

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## Senescent fibroblasts: Passive players or deliberate drivers of melanoma initiation and progression

We have developed a hybrid cellular automata model of skin that focuses on key variables implicated in the regulation of normal homeostatic skin function. The model consists of discrete cellular species such as melanocytes, transformed melanocytes, keratinocytes, and fibroblasts, and continuous microenvironmental variables such as growth factors and extracellular matrix. The behavior of each of the discrete cell species is defined using life cycle flowcharts. Based on our current biological understanding, we developed a cell-cell interaction network which defines local interactions between cells and their microenvironment. These local interactions lead to the emergence of *in vivo* normal skin structure.

Using our model, we first examined how robust it was to perturbations. The model not only recovers from massive loss of its constituents but also finds an equilibrium after super-physiological deviations in microenvironmental factors present in normal skin. However, when the model was perturbed by factors not typically present in normal skin, such as proteases, its robustness was dependent upon the duration of exposure. With long-term exposure skin was transformed to a pathologic state. This implies that the regulation of microenvironmental factors contributes to skin transformation from a normal to an abnormal state. When fibroblasts age they can become senescent and start producing factors that may disrupt the skin homeostasis. We incorporated these phenotypic changes into our model to examine how these changes affect skin function. Simulations show that senescent fibroblasts can stimulate melanocyte growth and invasion. We also integrated transformed melanocytes into the model and show that they can exploit stromal activation (or senescence) and change skin structure significantly. Model simulations also provide a series of virtual skin pathologies that readily recapitulate a spectrum of true aberrant clinical pathologies.

To validate our model predictions, we carried out several *in vitro* experiments that showed senescent fibroblasts enhance the growth of both melanocytes and early-stage melanoma cells. Furthermore, we found that senescent fibroblasts enhance melanoma migration almost twice as much as normal fibroblasts. Based on our integrated computational/experimental perspective, we speculate that senescent fibroblasts may create a pro-oncogenic environment that synergies with mutations to drive melanoma initiation and progression.

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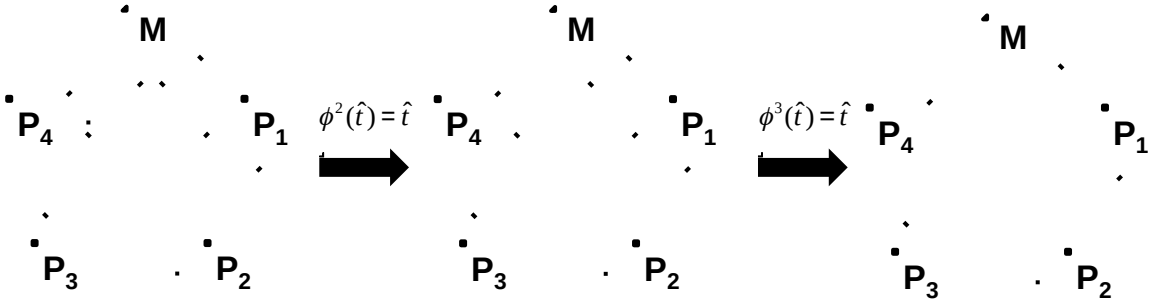
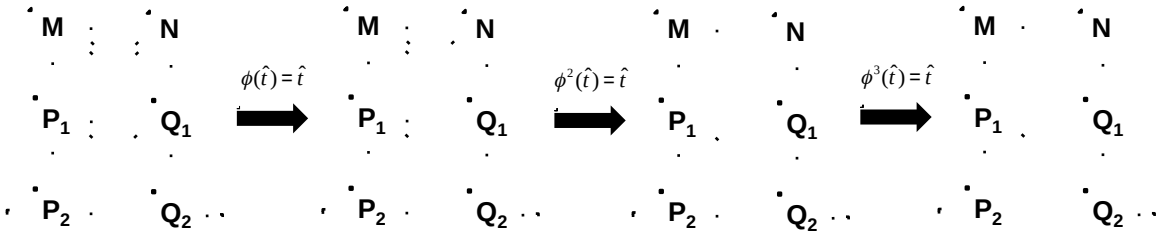
## On the Existence and Uniqueness of Biological Clock Models Matching Experimental Data

The development of luciferase markers and other experiment techniques has allowed measurement of the timecourses of the expression of genes and proteins with remarkable accuracy. Since this data has been used to construct many mathematical models, it is important to ask if this problem of model building is well-posed. Here, we focus on a common form of ordinary differential equation (ODE) models for biological clocks, which consist of production and degradation terms, and assume we have an accurate measurement of their solution. Given these solutions, do ODE models exist? If they exist, are they unique? We show that timecourse data can sometimes, but not always determine the unique quantitative relationships (i.e. biochemical rates) of network species. In other cases, our techniques can rule out functional relationships between network components and show how timecourses can reveal the underlying network structure. We also show that another class of models is guaranteed to have existence and uniqueness, although its biological application is less clear. Our work shows how the mathematical analysis of the process of model building is an important part of the study of mathematical models of biological clocks.

Example 1. Timecourses data reveals the structure of a single Goodwin oscillator.




Example 2. Timecourses data reveals the most structure of two independent Goodwin oscillators.



**MunJu Kim**, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
Katarzyna A. Rejniak, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

## The Role of Intracellular Mechanical Factors in Microtubule Bundling

Microtubules, the component of cell cytoskeleton, play versatile roles in different cellular processes, such as maintenance of cell structure, the backbone of intracellular transport, formation of the mitotic spindle, and reorientation of intracellular organelles. More importantly, some of their functions rely on the mechanical properties, such as the elasticity of microtubules or the way that microtubules interact with surrounding media. In this presentation we will discuss the microtubule bundling observed in circulating tumor cells after taxane-based chemotherapy. It is widely accepted that the tubulin stabilizing effect of taxanes is responsible for the bundling phenomena, and it is also suggested that the pattern of microtubule bundles may have potential prognostic value in assessing patient response to treatment. However, the underlying mechanisms are not clear and a variety of factors contributing to microtubule bundling need to be understood to better serve as a prognostic tool. We designed a computational model that captures mechanical behavior of growing microtubules in response to the tubulin stabilization, and tested computationally various cytoskeletal and morphological conditions to identify the possible mechanisms of microtubule bundling. Therefore, our model is able to establish a direct relationship between microtubule reorganization and taxane-based therapy.

## Title: The role of biomechanics in the breast cancer cell migration: A mathematical model

**Presenting author: Yangjin Kim**

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**Abstract**:

We investigated the role of microenvironment in an early development of Ductal carcinoma in situ (DCIS) and the invasion process in later stages. DCIS is an early stage non-invasive breast cancer that originates in the epithelial lining of the milk ducts, but it can evolve into comedo DCIS and ultimately the most common type of breast cancer, invasive ductal carcinoma. Understanding the progression and how to effectively intervene in it presents a major scientific challenge. The extracellular matrix (ECM) surrounding a DCIS tumor contains several types of cells and several types of growth factors that are known to individually affect tumor growth. However, the complex biochemical and mechanical interactions of stromal cells with tumor cells is poorly understood. The model can predict how perturbations of the local biochemical and mechanical state influence tumor invasion via crosstalk between a tumor and stromal cells such as fibroblasts. We present a hybrid invasion model where stromal cells play a significant role in triggering the invasion process of cancer cells from breast ducts. Our results shed light on the interactions between growth factors, mechanical properties of the ECM, and feedback signaling loops between stromal and tumor cells, and suggest how epigenetic changes in transformed cells affect tumor progression in the early and late stage of breast cancer. *joint work with Hans Othmer (University of Minnesota)

**Hristo V. Kojouharov**, The University of Texas at Arlington, Arlington, TX, USA
James P. Grover, The University of Texas at Arlington, Arlington, TX, USA
Laura D. Mydlarz, The University of Texas at Arlington, Arlington, TX, USA
Laura Gough, The University of Texas at Arlington, Arlington, TX, USA
Christopher Kribs-Zaleta, The University of Texas at Arlington, Arlington, TX, USA
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## Research-oriented education at the intersection of biology and mathematics: The undergraduate training in theoretical ecology research (UTTER) program

The goals of this NSF-funded research training program include enabling students from different academic disciplines to learn the concepts, language, and culture of another discipline, providing a substantive research experience at the intersection of ecology and mathematics, and encouraging members of underrepresented groups to pursue careers in biology and mathematics. Over two academic years, students take three special program courses, complete 4 semesters of a special seminar class, and take a summer research workshop. A team approach to teaching puts a biologist and a mathematician together in each class, so that instructors can meet biology and mathematics majors on their own terms and clarify critical terms and key concepts. Course activities are strongly project-oriented: topics are introduced that serve as course projects and provide open questions leading to research. Student research projects have also been enriched by seminars focused on mastering published research literature, which also provide guest visits by established researchers, and by workshops emphasizing research, analytical, computational, and presentation skills.

Many of the practices being developed will be carried into a new Mathematical Biology option for the undergraduate degree program in Mathematics, and can serve as a model for cross-fertilizing the disciplines of biology and mathematics. Assessments to date indicate that students are enthusiastic about team-taught, interdisciplinary coursework, opportunities to conduct research, and other enrichments of the academic experience.

# Ecological Complexity and Biodiversity Maintenance

**Michio Kondoh**
Dept. of Environmental Solution Technology, Ryukoku Univ., Otsu, Japan
Akira Okubo Prize Talk

An ecological community can be viewed as a network of interacting species, where various interspecific effects are transmitted and propagate over the community to drive community-level dynamics. Community complexity, often captured by species diversity and complex interactions between them, is a characterizing feature of real ecological communities, but theory often predicts that such complexity could make a community more fragile. This being so, what maintains species diversity in the natural, complex communities? In this talk I would like to focus on possible theoretical mechanisms for biodiversity maintenance and on the predicted role of ecological complexity in those theories. Interaction flexibility and diversity in interaction types will be of particular focus as the factors that potentially reverse the classically negative complexity effect to biodiversity maintenance into a positive one.

**Adam Koss**, University of Illinois Urbana-Champaign, Urbana, IL, USA
Glynn Davis, University of Illinois Urbana-Champaign, Urbana, IL, USA
Sarah Duple, University of Illinois Urbana-Champaign, Urbana, IL, USA
Ping Lee, University of Illinois Urbana-Champaign, Urbana, IL, USA
Zoi Rapti, University of Illinois Urbana-Champaign, Urbana, IL, USA
Carla Caceres, University of Illinois Urbana-Champaign, Urbana, IL, USA
Meghan Duffy, Georgia Institute of Technology, Atlanta, GA, USA
Spencer Hall, Indiana University, Bloomington, IN, USA

## Interspecific competition for algal resources alters disease dynamics in *Daphnia*

Species other than the host and parasite (predators, competitors, resources) can alter disease spread. Using a tractable disease (the fungus Metschnikowia bicuspidata and its host Daphnia dentifera) we explore the direct and indirect effects on the host population. We integrate the role of Daphnia as grazers of algae, competitors with other zooplankton, and as prey to investigate the effects these roles play on the contraction of the disease. For instance, the rate at which hosts consume food (and fungal spores) and move it through their gut depends on body size, genotype and food levels. Gut passage time influence disease susceptibility, because Daphnia become infected when fungal spores puncture the gut wall. Resources, which are determined in part by competitors, influence the production of infective forms of the parasite. Other planktonic competitors consume but do not produce infective forms of the parasite, hence may reduce disease via a dilution effect. As prey the Daphnia can be eaten by fish such as Bluegill which consume the daphnia whole and remove the spore from the population. They also hunt the infected at a higher rate due to the color difference in daphnia. Another predator *Chaoborus* are sloppy eaters and while eating the daphnia release the spores back into the population. We do not include this sloppy eating into our model. We integrate a mathematical model for the nonlinear interactions of five populations (susceptible hosts, infected hosts, parasite spores, algae, diluters) with laboratory experiments and field data from epidemics occurring in Midwestern lakes. The model consists of a system of five coupled ordinary differential equations.

We find signatures of a dilution effect influencing prevalence of Metschnikowia bicuspidata in Daphnia dentifera in Midwestern lakes. Years with smaller epidemics often had increased abundances of other Daphnia species relative to D. dentifera. In addition, within a season, increasing densities of D. pulicaria were often correlated with declining prevalence of Metschnikowia. The field data suggest that disease dynamics are likely influenced both by D. pulicaria consuming spores but not becoming infected (i.e., acting as a diluter) and D. pulicaria altering resources (i.e., acting as competitor). Laboratory measurements of gut passage time for both species have revealed striking differences between the two species, and among genotypes within each species. Gut passage time ranges from a few minutes to almost a half an hour, depending on the species, genotype, body size, and food level. This difference in gut passage time may help to explain the observed differences in susceptibility among species, genotypes and environmental conditions that we have observed. We have also analyzed the seven biologically meaningful equilibria and performed a stability analysis. Several bifurcations depending on the parameter values have been found.

**Roberto A. Ku**, Centro de Investigacion en Matematicas, Guanajuato, GTO, MEX
Francisco J. Solis, Centro de Investigacion en Matematicas, Guanajuato, GTO, MEX

## Nonlinear Juvenile Predation Population Dynamics

A general nonlinear age-structure predator-prey model is analyzed for the dynamics of two interacting populations that includes self-limitation on the prey and juvenile predation. Our aim is to identify mechanisms of newborn survival that allow us to explain viable interactions between the two populations in circumstances when their absence would otherwise result in unstable behavior with unbounded oscillations. To achieve our goal we apply some standard methods in the analysis of dynamical systems such as Painlevé and bifurcation analysis.

## Title: From Discrete to Continuous Models of Cell Movement: an Application to Medical Implants

**Presenting author: Alicia Prieto Langarica**

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**Abstract**:

Mathematical modeling of cell movement is needed to aid in the deeper understanding of vital processes such as embryogenesis, angiogenesis, tumor metastasis and immune reactions to foreign bodies. In this work, we develop multiscale models of cell movement in response to external stimulus, incorporating both a random and a biased component. In order to model the random nature of the movement, an individual based (IBM) model is created to simulate cells moving in the presence of a heterogeneously distributed stimulus molecules. The discrete IBM model is then upscaled, starting with transition probabilities of the individuals at each site, to obtain a corresponding continuous differential equation (DE) model. Continuous models allow for a more general study of larger domains. Under traditional modeling assumptions the proposed new models reduce to previously developed models in the literature. Next, we present a set of numerical experiments which show very good agreement between the new continuous DE and discrete IBM models for a variety of different values of the parameters. Furthermore, applications of the new mathematical models to infection control on medical implants are also presented.

**Glenn Ledder**, University of Nebraska - Lincoln, USA

## An Optimization Model that Links Masting to Seed Herbivory

Masting is a life history strategy whereby perennial plants have one or more years of little or no reproduction, punctuated by years with massive reproduction events. The literature on masting focuses on description of this behavior, particularly the common observation that individuals in a population act in synchrony. To date, there is no published work that connects masting to characteristics of the ecological niche of the plant species, such as the overall growing capacity or the extent of seed herbivory. In this study, we develop a resource-based optimization model with seed herbivory risk as a key parameter, and we show that the optimal strategy for such a scenario can be periodic masting, with the masting interval an increasing function of seed herbivory risk. In particular, this model suggests one possible reason why a species of conifer in Norway exhibits a masting cycle of two years in part of the country and a cycle of three years in another part.

## Using Virtual Laboratories to Teach Mathematical Modeling

**Glenn Ledder**
Department of Mathematics, University of Nebraska-Lincoln

Mathematical modeling encompasses a richness that is not well captured by the prepackaged application topics in textbooks. As the "tendons that connect the muscles of mathematics to the bones of science," modeling requires a connection to the scientific enterprise--a connection that must incorporate observation of scientific experiments, collection of scientific data, and scientific interpretation of modeling results. Unfortunately, real biological experiments conducted in the real world take a significant amount of time and require a combination of good design, technique, and luck. Some innovators have tried to incorporate such experiments into a mathematics course, with varying degrees of success that depend inversely on the richness of the biological and mathematical content. In this talk, we present the BUGBOX virtual laboratories created by the author for the purpose of providing real observational and experimental experiences in a virtual world. The experiments can be conducted quickly and easily using software originally written in Python and converted to Windows executable files. Because of the complete flexibility of virtual world design, the BUGBOX laboratories pose modeling problems without the complication of procedure and measurement problems. BUGBOX-predator is a computerized recreation of a simulated experiment used by C.S. Holling in a landmark 1959 paper to develop models for the effect of prey density on predation rates. The virtual environment includes three different virtual species of predator, providing a simple beginning and the necessary insights to develop more sophisticated models from mechanistic assumptions. BUGBOX-population is an experiment designed to illustrate the phenomena and modeling of stage-structured population growth. Students develop discrete linear growth models for a sequence of four increasingly realistic species of virtual insect; the development requires observation to determine the correct mechanistic assumptions and measurement of parameter values. With a directed approach to analysis of the model, students are led to discover the physical solution features that correspond to the mathematical concepts of eigenvalues and eigenvectors.

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Joshua S. Weitz, School of Biology & School of Physics, Georgia Institute of Technology, Atlanta, GA, USA
Harold D. Kim, School of Physics & School of Biology, Georgia Institute of Technology, Atlanta, GA, USA

## Quantifying the interaction between neighboring gene circuits in *Saccharomyces cerevisiae*

Gene regulation is typically described in terms of the recruitment of transcriptional machinery to genes in order to transcribe RNA from DNA. In this view, transcriptional rates depend on the availability of specific biomolecules called transcription factors, which help recruit and stabilize RNA polymerase, the enzyme responsible for transcription, to the start site of genes. However, recent experimental observations have noted that gene regulation can also be affected by the spatial location of genes in the genome[1,2]. Indeed, adjacent genes in the eukaryotic genome interact to give rise to unique properties. For example, adjacent genes often show stronger correlation in temporal dynamics and higher gene expression level than when they are expressed alone[3,4]. Recent studies in prokaryotes have demonstrated various modes of interaction between adjacent genes (e.g. transcriptional interference), but they cannot account for the unique properties of adjacent genes in eukaryotes. In addition, genome-wide studies in eukaryotes have proposed potential mechanisms for interaction between adjacent genes, but a quantitative understanding of gene-gene interaction remains unclear.

In this study we utilized a combined experimental and theoretical approach to study the interaction between adjacent genes in eukaryotes. We synthesized manipulable genetic circuits comprised of the constitutive KlURA3 promoter (pURA) juxtaposed to the inducible GAL1 promoter (pGAL1) in various arrangements. pGAL1 undergoes a change in chromatin state upon induction, while the chromatin state of pURA is expected to be fixed. Taking advantage of these properties, we quantified how pURA activity is affected by the chromatin state of pGAL1 when the two promoters are oriented in various arrangements.

Our experimental results showed distinct patterns in pURA activity between uninduced and induced conditions, but only when the two promoters are juxtaposed in a bidirectional manner. We observed that the activity of bidirectionally oriented pURA was significantly repressed when pGAL1 was uninduced. Similarly, we observed a drastic increase in pURA activity when pGAL1 was induced. In contrast, our results showed that pGAL1 activity remained constant regardless of the relative arrangements, suggesting that the chromatin state of pGAL1 (but not pURA) is well protected from the neighboring chromatin domains. Our results together demonstrate that functionally unrelated genes that are juxtaposed can be transcriptionally coupled, providing an explanation for the unique properties of adjacent genes. Based on these results, we build a rate-equation based model of transcriptional interactions along the genome. This rate equation model considers multiple states of individual promoters. State transitions within a promoter are then governed by the state of promoter itself and that of adjacent promoters. We utilize this rate equation based model to highlight possible mechanisms and consequences of promoter interaction.

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# Stationary distributions of semistochastic processes with disturbances at random times and with random severity

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*Keywords: Ecology, Ecosystems*

Mathematical modeling can play an important role in understanding and predicting phenomena in natural sciences. In this talk we will discuss the role of mathematical models in describing and understanding disturbance and recovery regimes of systems. We will consider a mathematical model for a semi-stochastic continuous-time continuous-state space random process that undergoes downward disturbances with random severity occurring at random times. Between two consecutive disturbances the evolution is deterministic, given by an autonomous ordinary differential equation. This model allows the derivation of explicit expressions for several quantities of interest, providing important information on the behavior of the system. In particular, we derive explicit expressions for distributions connecting two consecutive post-disturbance levels, stationary distribution of the post disturbance levels as well as the stationary distribution of the random process.

# When should a trophically and vertically transmitted parasite manipulate its intermediate host? The case of *Toxoplasma gondii*

**Maud Lélu**[1], Michel Langlais[2], Marie-Lazarine Poulle[3,4], Emmanuelle Gilot-Fromont[5, 6 *], Sylvain Gandon[7 *]
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[7] Centre d'Ecologie Fonctionnelle et Evolutive, CNRS–UMR5175, Montpellier, France.

## Abstract

Parasites with complex life cycles are expected to manipulate the behavior of their intermediate hosts (IHs) to increase their predation rate and facilitate the transmission to definitive hosts (DHs). This strategy, however, is a double-edge sword when the parasite can also be transmitted vertically in the IH. In this situation, the manipulation of the IH behavior, which increases the IH death rate, conflicts with this second route of transmission which requires healthy and reproducing IHs. The protozoa *Toxoplasma gondii*, a wide spread pathogen, combines both trophic and vertical transmission strategies. Is parasite manipulation of host behavior still adaptive in this situation? We model the evolution of the IH manipulation by *T. gondii* and study the conflict between these two routes of transmission under different epidemiological situations. We show that the evolutionary outcome of this conflict depends on the level of virulence and vary between early and later stages of an epidemic: manipulation is particularly advantageous for virulent strains and in epidemic situations. In addition, we show that different levels of manipulation may evolve depending on the sex of the IH: the intensity of manipulation is expected to be higher in males than in females. These results may help to understand the variability of strain characteristics encountered for *T. gondii* and may extend to other trophically transmitted parasites.

## A beginning mathematics course to train the new biologists

**Suzanne Lenhart**
Department of Mathematics, University of Tennessee, Knoxville, TN, USA

Basic concepts and tools in our course, `Mathematics for the Life Sciences,' will be presented. This course is designed to train the future `new biologists,' undergraduate students with a broad spectrum of majors, connected with the life sciences. The goals and methods include

- Develop a student's ability to quantitatively analyze problems arising in biological areas.
- llustrate the utility of mathematical models to provide answers to key biological problems.
- Develop an appreciation of the diversity of mathematical approaches potentially useful in the life sciences.
- Provide experience using computer software to analyze data, investigate mathematical models and provide some exposure to programming.

The course starts with statistics, discrete models and probability, and then calculus concepts come in the second semester. The text for this course is being developed by Erin Bodine, Louis Gross and Suzanne Lenhart.

**Herbert Levine**, Rice University, Houston TX, USA

## Models of Moving Cell Morphologies

Cell migration is a pervasive process in many biology systems and involves protrusive forces generated by actin polymerization, myosin dependent contractile forces, and force transmission between the cell and the substrate through adhesion sites. Here we develop a computational model for cell motion that uses the phase field method to solve for the moving boundary with physical membrane properties. It includes a reaction-diffusion model for the actin-myosin machinery and discrete adhesion sites which can be in a "gripping" or "slipping" mode and integrates the adhesion dynamics with the dynamics of the actin filaments, modeled as a viscous network. To test this model, we apply it to fish keratocytes, fast moving cells that maintain their morphology, and show that we are able to reproduce recent experimental results on actin flow and stress patterns. Furthermore, we explore the phase diagram of cell motility by varying myosin II activity and adhesion strength. Future work will focus on extending this model to encompass the pseudopod-dominated motility seen in Dictysotelium amoebae and in human neutrophils.

**Sivan Leviyang**, Georgetown University, Washington, DC, USA

## Computational Approaches to the Population Genetics of Early HIV Infection

During HIV infection, the immune system mounts a vigorous response in the form of T cell and antibody attack. In early HIV infection, this response has been shown to be a significant selective force on the infecting HIV population. Through mutation, the HIV population can escape such selection.

From a population genetics perspective, modeling early HIV infection posses significant challenges. The immune system mediated selection is complex, HIV mutation rates are high, and the dynamics of the HIV population are non-linear. The combination of these issues in a single model raises many novel theoretical and computational population genetics related questions.

In this talk I will discuss a population genetics model of early HIV infection. Using this model as a basis, I will then discuss several computational approaches that can be used to investigate the nature of HIV evolution under immune system attack during early infection.

**Doron Levy**, University of Maryland, College Park, MD, USA

## Mathematical Models for Tumor-Immune Interactions and Their Applications

In this talk we will describe our recent mathematical models of the interaction between the immune system and cancer focusing on two specific components: TGF-$\beta$ and B7-H1. TGF-$\beta$is an immunoregulatory protein that contributes to inadequate antitumor immune responses in cancer patients. Recent experimental data suggests that TGF-$\beta$ inhibition alone, provides few clinical benefits, yet it can significantly amplify the anti-tumor immune response when combined with a tumor vaccine. We develop a mathematical model in order to gain insight into the cooperative interaction between anti- TGF-$\beta$ and vaccine treatments. We show that our model is capable of capturing the observed experimental results, and hence can be potentially used in designing future experiments involving this approach to immunotherapy.

The second part of the talk will be devoted to the surface protein B7-H1. B7-H1 is found on carcinomas of the lung, ovary, colon, and melanomas but not on most normal tissues. B7-H1 has been experimentally determined to be an antiapoptotic receptor on cancer cells, where B7-H1-positive cancer cells have been shown to be immune resistant, and *in vitro* experiments and mouse models have shown that B7-H1-negative tumor cells are significantly more susceptible to being repressed by the immune system. We derive a new mathematical model for studying the interaction between cytotoxic T cells and tumor cells as affected by B7-H1. By integrating experimental data into the model, we isolate the parameters that control the dynamics and obtain insights on the mechanisms that control apoptosis. This is a joint work with Amanda Galante, Shelby Wilson, and Koji Tamada.

**Aaron Lim**, Centre for Mathematical Biology, Oxford University, Oxford, UK
Sunetra Gupta, Department of Zoology, Oxford University, Oxford, UK
Philip Maini, Centre for Mathematical Biology, Oxford University, Oxford, UK

## HTLV-I Infection: A Dynamic Struggle Between Viral Persistence and Host Immunity

Human T-lymphotropic virus type I (HTLV-I) is a persistent human retrovirus characterised by life-long infection and risk of developing one of two major, clinically independent diseases: adult T-cell leukaemia/lymphoma (ATL), an aggressive blood cancer, and HAM/TSP, a progressive neurological and inflammatory disease. Infected individuals typically mount a large, chronically activated $CD8^+$ cytotoxic T-lymphocyte (CTL) response against HTLV-I-infected cells, but ultimately fail to effectively eliminate the virus. Moreover, identification of determinants to disease manifestation has thus far been elusive.

A key issue in current HTLV-I research is to better understand the dynamic interaction between persistent infection by HTLV-I and virus-specific host immunity. Recently, Asquith and Bangham [1] have proposed an experimental hypothesis for the persistence of HTLV-I *in vivo* which has motivated the formulation of a mathematical model by Li and Lim [2] that illustrates the balance between latency and activation in the target cell dynamics of the viral infection. We present an extension of this previous model that incorporates the role of a constantly changing anti-viral immune environment mediated by HTLV-I-specific CTLs. The resulting model is a four-dimensional system of ordinary differential equations that describes the dynamic interactions among viral expression, infected target cell activation, and the HTLV-I-specific CTL response.

We have identified a sharp threshold parameter, the basic reproduction number for viral infection $R_0$, which completely characterises the global behaviour of solutions to the model: if $R_0 < 1$, the infection is cleared; if $R_0 > 1$, the infection is chronic. The global stability of the respective equilibrium state in each of the two cases for $R_0$ has been shown by constructing appropriate Lyapunov functions.

Having established the global dynamics of the model, we set out to address biologically relevant questions in the case of chronic HTLV-I infection. In particular, we focussed on three issues: (i) How is the virus able to evade CTL-mediated elimination and not only establish, but also maintain, infection? (ii) What role do CTLs play in controlling the virus? (iii) Do our results provide insights to the development of HTLV-I-associated disease?

Using bifurcation analysis and computational methods, we explored the roles of certain key parameters on the outcome of the infection dynamics. The results of our investigation offer important insights to the evolution of viral persistence and proposes a hypothesis for pathogenesis.

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## Mechanism of cell polarization in budding yeast

**Rong Li**
Stowers Institute for Medical Research, Kansas City", MO, USA

The establishment of cell polarity is a critical step in the generation of cell shape, cell motility, and asymmetric cell division during diverse developmental and physiological processes. A conserved regulator of cell polarity in eukaryotes is the Rho-family GTPase, Cdc42. Work in the past ten years or so has demonstrated that the establishment of cell polarity to be driven by two coupled mechanisms: one involving actin assembly and actin-based transport, and the other independent of actin but requiring cytosolic chaperoning of Cdc42 by the GDI protein. The resulting polarized state is dynamic and must be maintained through active Cdc42 recycling. The parameters of recycling influence the shape of Cdc42 distribution and morphogenetic outcome. In this presentation, I will discuss our recent results on an unexpected role for membrane diffusion property of Cdc42 in the establishment stable cell polarity.

## Dynamics of a vesicle in viscous fluids

**Shuwang Li**, Kai Liu

Applied Math Department, Illinois Institute of Technology, Chicago

Recent experimental results on giant unilamellar vesicles (GUVs) show that mixed multiple lipid components on the surface of a membrane may decompose into coexisting phases with distinct compositions, with concomitant changes in the surface morphology. The driving forces for the evolution involve line tension along the phase boundaries, inhomogeneous surface/bending energy, and fluid forces. Here we are interested in exploring the emergent morphologies of a vesicle in shear flow and in extensional flow. In this talk, I will present the modeling and computation of a multicomponent vesicle and study its dynamics in viscous flow. Our numerical results suggest that the nonhomogeneous surface tension/bending, together with the flow, introduces nontrivial dynamics including locomotion, budding, tumbling and wrinkling.

## Energetic Variational Approaches in the Modeling of Ionic Solutions and Ion Channels

**Chun Liu**
Penn State University

Abstract: Ion channels are key components in a wide variety of biological processes. The selectivity of ion channels is the key to many biological process. We try to study these selectivity mechanisms in ion channels by developing reduced models, taking into consideration of dielectric coefficient and ion particle sizes, as well as their very different, however primary, structures and properties. These self-organized systems will be modeled and analyzed with energetic variational approaches (EnVarA) that were motivated by classical works of Rayleigh and Onsager. The resulting/derived multiphysics-multiscale systems automatically satisfy the Second Laws of Thermodynamics and the basic physics that are involved in the system. In this talk, I will discuss some of the related issues we had encountered in these projects.

Jane M. Heffernan, **Yijun Lou** and Jianhong Wu
Mprime Centre for Disease Modelling, York Institute of Health Research, Toronto, Ontario
Department of Mathematics and Statistics, York University, Toronto, Ontario, Canada

## Cost-effectiveness Evaluation of Vaccination Programs Against Sexually Transmitted Diseases for Different Sexes

For sexually transmitted diseases the determination of an optimal vaccination program is not straightforward due to sexual heterogeneity since (1) the transmission probabilities between two different sexes are normally unequal (weighted to a greater probability from males to females than vice versa), (2) demographic parameters between the two sexes are unequal, (3) the prevalence of disease in one sex may have a greater impact on the morbidity and mortality of the next generation (transmission to the neonate).

In this talk, we will present two models of sexually transmitted infections (with and without age structure) to evaluate the cost-efficacy of vaccination programs for different sexes in the context of sexually transmitted disease control, with special application to potential genital herpes vaccination programs. For both models, we find that the stability of the system and ultimate eradication of the disease depend explicitly on the corresponding reproduction number. We also find that vaccinating females is more cost-effective, providing a greater reduction in disease prevalence in the population and the number of infected females of childbearing age. This result is counter-intuitive since vaccinating super-transmitters (males) over sub-transmitters (females) usually has the greatest impact on disease prevalence. Sensitivity analysis is implemented to investigate how the parameters affect the control reproduction numbers and infectious population sizes.

**Sarah Lukens**, Dept. of Mathematics, University of Pittsburgh, Pittsburgh, PA
David Swigon, Dept. of Mathematics, University of Pittsburgh, Pittsburgh, PA
Gilles Clermont, Dept. of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA

## Ensemble modeling of symptoms to human immune response of Influenza A virus infection

Deterministic models of a host-level response to influenza A virus (IAV) infection assume a perfect prediction, while an ensemble approach may account for patient and strain variability, and uncertainty in data used to calibrate the models. We generate an ensemble of parameter sets that represent a calibration to experimental data of viral titers and symptoms measured in humans with IAV infection to a host-level model with innate and adaptive immunities. Systemic, upper respiratory and lower respiratory symptoms are mapped to model interferon levels, and extent of upper and lower respiratory cells damage. In order to differentiate between upper and lower symptoms, we compartmentalize the respiratory tract into upper and lower compartments. We measure clinical factors such as onset and severity of symptoms across our ensemble distribution and obtain biologically relevant distributions while also achieving variability in host responses. Sensitivity analysis across the parameter ensembles is employed in order to characterize population-scale relevant clinical phenotypes (severity of infection, immunogenicity) to model kinetic parameters.

**Dori Luli**, Arizona State University, Tempe, AZ, USA
Sharon Crook, Arizona State University, Tempe, AZ, USA

## A Neuronal Network Model of *Drosophila* Antennal Lobe

Olfaction is an important sensory modality for behavior since odors inform animals of the presence of food, potential mates, and predators. The fruit fly, *Drosophila melanogaster*, is a favorable model organism for the investigation of the biophysical mechanisms that contribute to olfaction because its olfactory system is anatomically similar to but simpler than that of vertebrates. In the *Drosophila* olfactory system, sensory transduction takes place in olfactory receptor neurons housed in the antennae and maxillary palps on the front of the head. The first stage of olfactory processing resides in the antennal lobe, where the structural unit is the glomerulus. There are at least three classes of neurons in the antennal lobe - excitatory projection neurons, excitatory local neurons, and inhibitory local neurons. The arborizations of the local neurons are confined to the antennal lobe, and output from the antennal lobe is carried by projection neurons to higher regions of the brain.

Different views exist of how circuits of the *Drosophila* antennal lobe translate input from the olfactory receptor neurons into projection neuron output. Some imaging studies show that the activation of a post-synaptic projection neuron reflects the activation of the associated pre-synaptic olfactory receptor neurons; however, electrophysiological studies suggest that projection neurons are more broadly tuned than olfactory receptor neurons, and that projection neuron output is shaped by both olfactory receptor neuron input and by lateral connections within the antennal lobe [Bhandawat et al., 2007]. A study of optical recordings of glomerular calcium responses suggests the existence of both a glomerulus specific network, which includes excitatory and inhibitory local connections, and a global inhibitory network that acts on all glomeruli [Silbering and Galizia, 2007]. Recent studies suggest that excitatory local neurons recruit inhibition and spread excitation between projection neurons in different glomeruli; while inhibitory local neurons facilitate gain control [Wilson, 2011].

We construct a conductance based neuronal network model of the *Drosophila* antennal lobe with the aim of proposing possible interactions within the antennal lobe that account for the variety of projection neuron activity observed in experimental data. First, we develop realistic minimal cell models for the excitatory local neurons, inhibitory local neurons, and projections neurons based on experimental data for *Drosophila* channel kinetics. These single cell models exhibit Type II dynamics at the transition to repetitive firing. The inhibitory local neuron model exhibits regular repetitive firing in the presence of stimulus, and the projection neuron model exhibits repetitive firing but of higher frequency than the inhibitory local neuron in the presence of stimulus. The excitatory local neuron exhibits bursting in the presence of some stimuli. We then investigate possible inter- and intra-glomerular connectivity patterns in the *Drosophila* antennal lobe, where olfactory receptor neuron input to the antennal lobe is modeled with Poisson spike trains, and synaptic connections within the antennal lobe are mediated by chemical synapses and gap junctions as described in the *Drosophila* antennal lobe literature. Computational studies using olfactory receptor neuron inputs that mimic experimental recordings demonstrate the possible roles of excitatory local neurons in spreading excitation among glomeruli and in recruiting inhibition.

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**Siding Luo**, Department of Civil Engineering, University of Glasgow, UK
Christopher Quince, University of Glasgow, UK

## Deterministic and Stochastic Density-Dependent Population Process in Chemostat Model

The well-known mathematical model of a chemostat is an explicit resource model to analyse the competitive density-dependent population process. It has been given broad applications in microbiology. In our model, a chemostat model with Monod kinetics, two species and single limiting resource is given. These species are defined as quasi-neutral when they require the same resource concentration at equilibrium. The deterministic model is used to derive a stochastic model by assuming the birth and deaths follow a Poisson process. With the consideration of infinity volume $V$(in units of volume of cell), we pass the discrete model to a continuous limit. Several limit theorems are presented in our model to approximate and characterize the Markov process.

We will present the deterministic model approximated by the Law of Large Numbers, and analyse the stability of its equilibrium state. After the process approaches the neighbourhood of the equilibrium state, it will behave approximately as a diffusion process along with the equilibrium state. With the help of Central Limited Theorem, Ito's formula and Thomas Kurtz's weak convergence theorem, when the initial condition is in longer-scale, rigorous proofs will be presented for the diffusion approximation maps onto deterministic trajectory. To get this diffusion approximation, the derivatives of projection map will be calculated, which part is based on Dr. Todd Parsons's work.

The calculation of Fixation probability and extinction times is a consequence of the above diffusion approximation result, driven by the formulation of infinitesimal generator $A$ of the diffusion process, with the form of $Af(p) = b(p)\frac{df}{dp} + \frac{1}{2}a(p)\frac{d^2f}{dp^2}$ and initial relative abundance of one species, $p$. We will present the results for the fixation of this species, mean first absorption time, and the expected time to fixation in the function set of $f$.

Lastly, we verify our approximations by comparison with exact numerical computations, and we investigate the accuracy of our approximations at small population size over a range of parameters.

**Wes Maciejewski**, Queen's University, Kingston, Ontario, Canada

## The Role of Vertex Degree in Evolution on Graphs

Since their introduction a decade ago, evolutionary graphs are now a well-studied representation of structured populations. They have proven to be valuable in the investigation of the evolution of cooperative social behaviours. The exact features of graphs that promote, or work against, cooperation are, however, still elusive. There has been some interest in the role of vertex degree. Some work has shown that highly connected vertices act as promoters of cooperation while other work has shown this for those with less connections. The goal of my current work is to better understand the role of degree in evolutionary processes on graphs. I adapt the concept of reproductive value to the study of evolutionary graphs which aids in addressing which nodes are conducive to cooperation and when. I propose the simple rule: evolution is promoted on vertices with the highest reproductive value, regardless of population regulation process.

As a companion to this result, I present an example that demonstrates that arguments based solely on degree are insufficient for explaining the emergence of cooperation on graphs. It is possible for a graph to have vertices all of the same degree (ie. a regular graph) yet experience location-dependent levels of cooperation. This example emphasizes the importance of the underlying graph topology in the evolutionary process.

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*Shannon Mumenthaler*, CAMM, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
*Lee B. Jordan*, Department of Pathology, NHS Tayside / University of Dundee, Dundee, UK
*Colin A. Purdie*, Department of Pathology, NHS Tayside / University of Dundee, Dundee, UK
*Andrew J. Evans*, Surgical and Molecular Oncology, University of Dundee, Dundee, UK
*David B. Agus*, CAMM, Keck School of Medicine, University of Southern California, Los Angeles, CA
*Alastair M. Thompson*, Surgical and Molecular Oncology, University of Dundee, Dundee, UK

## Integration of Pathology, Radiology, and *in vitro* Data in Patient-Calibrated Cancer Simulations: Recent Advances and Future Outlook for Ductal Carcinoma In Situ (DCIS)

Ductal carcinoma in situ (DCIS), a significant precursor to invasive ductal carcinoma, is commonly detected as a subtle pattern of calcifications in mammograms. Such radiologic imaging is used to plan surgical resection of the tumor, but multiple surgeries are often required for complete excision. Pathologists use pre-surgical biopsies to stage the DCIS and help choose therapies. Some investigations are developing molecular profiling to help stratify patients and select therapeutic agents. For DCIS and more broadly in clinical oncology, there is currently no technique to quantitatively combine these diverse data sources to improve surgical and therapeutic planning; such planning generally also cannot incorporate novel *in vitro* measurements. Mechanistic, patient-calibrated computational models may provide a quantitative link between multiple patient data types, provides a platform for testing leading cancer biology hypotheses, and could help to extrapolate *in vitro* experimental findings to likely *in vivo* tumor behavior in individual patients.

We have recently developed a biologically-grounded agent-based model of tumor cells, where cell motion is determined by biomechanical forces, phenotype is controlled by microenvironment-dependent stochastic processes, and detailed phenotype sub-models describe cell volume changes, including the first model of cell calcification [1]. This work introduced the first patient-specific calibration to pathology data from a single time point (e.g., from a biopsy), and predicted DCIS growth rates and mammography-pathology size correlations; all predictions were quantitatively consistent with the clinical literature. We recently combined this work with a coarse-graining method to calibrate a continuum model of patient-specific DCIS surgical excision volumes; the predictions were reasonably successful in 14 of 17 test cases [2]. We are currently performing extensive, phenotype-specific *in vitro* time-course measurements of cell volume in breast cancer cell lines, allowing model refinements and more accurate simulation of emergent tumor behavior [3]. In an ongoing validation study, we are calibrating this refined model to predict patient-specific DCIS growth rates and mammography-pathology correlations in 5-10 patients, with validation against each patient's mammographic imaging [4]. All these pieces point to a day when mechanistic models are refined and constrained by *in vitro* measurements of relevant standardized or primary (patient-derived) cell lines, calibrated to patient pathology and other molecular profiling, and used to predict growth rates and estimate spatially-varying optimal surgical margins that surgeons can overlay on mammographic imaging. We close by discussing the wider outlook for patient-specific simulations beyond DCIS. We anticipate that such efforts will play an increasing role in driving experimental cell biology, testing and challenging current cancer biology orthodoxy, and ultimately improving clinical care.

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**Bruce MacLennan**, University of Tennessee, Knoxville, TN, USA

## Mathematical Principles of Morphogenesis Applied to Nanoscale Self-Assembly

Our research is applying the mathematical principles of embryological morphogenesis to the self-assembly of complex, hierarchically structured physical systems. Current approaches to nanoscale self-assembly are limited to homogeneous or highly regular structures. On the other hand, future applications of self-assembly (such as sophisticated autonomous robots) will require the ability to assemble physical systems that are structured from the nanoscale up to the macroscale. The best example we have of such a process is morphogenesis in the developing embryo.

Our approach is to take known or hypothesized processes of biological morphogenesis, to extract their mathematical structures, and to apply them to the synthesis of artificial systems. Our goal is to develop morphogenetic algorithms that apply to very large numbers of agents (hundreds of thousands to hundreds of millions), and so we use partial differential equations (PDEs) as our primary expressive medium (as is also common in the biological morphogenesis literature). In order to accommodate the visco-elastic properties of large numbers of connected microscopic agents, we use the theoretical framework of continuum mechanics in a Lagrangian reference frame. One goal is to develop techniques that mimic or replace the fundamental morphogenetic processes described by Salazar-Ciudad, Jernvall, and Newman (2003).

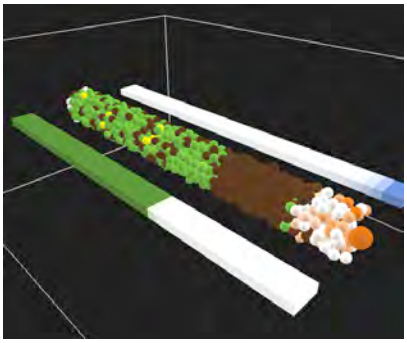

Figure 1: Clock-and-Wavefront Process

As one particular case we have extracted documented morphogenetic processes out of their biological developmental context, and applied them to the simulated synthesis of a complex structure: a segmented "spine" with a opposed pairs of segmented "legs." To accomplish this we have applied the "clock and wavefront" process of Cooke and Zeeman (1976) to generate both the spine — which is analogous to embryological somitogenesis — but also to the generation of the legs. By controlling the parameters of the process we can independently control the number and length of the segments of both the spine and the legs. The legs grow out of imaginal disks whose placement is controlled by morphogen gradients from the anterior and posterior boundaries of the spinal segments.

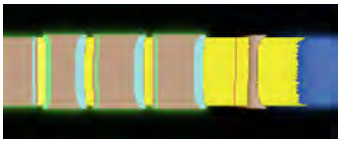

Figure 2: Development of Spine

To facilitate the description of morphogenetic processes, whether implemented by biological or artificial agents, we have developed a sort of programming language suited to the description of "tissues" composed of differing substances characterized by their properties and active behavior, defined by stochastic PDEs. The formal properties of the notation permit the equations to be implemented in a variety of physical media, both living and nonliving.

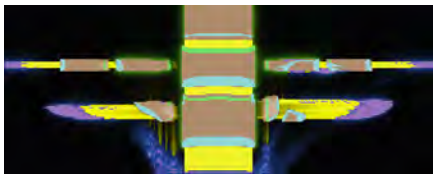

Figure 3: Development of Legs

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**Gesham Magombedze**, National Institute for Mathematical and Biological Synthesis, University of Tennessee, Knoxville,TN, USA.
Vitaly V. Ganusov, Department of Microbiology, University of Tennessee, Knoxville, TN, USA.
Shigetoshi Eda, Department of Forestry, Wildlife and Fisheries, University of Tennessee, Knoxville, TN, USA.

## Assessment of Th1/Th2 immune response paradigm in *Mycobacterium avium subspecies paratuberculosis* infections.

Johne's disease, a persistent and slow progressing infection in ruminants such as cows and sheep is caused by *Mycobacterium avium subspecies paratuberculosis* (MAP) bacillus. Mycobacterial infections are associated with complex immune response mechanisms whose underlying biology is not clearly understood. Host immune response to MAP infection is associated with predominance of a cell mediated response in its early stages (Th1) and a switch to the dominance of antibody response (Th2) which is associated with rapid disease progression. How this switch is achieved during the infection and whether such switch can be regulated remains poorly understood. In this study, we develop several mathematical models to understand the driving causes for Th1 to Th2 switch in MAP infection. We specifically consider two hypotheses: 1) switch is driven by accumulation of extracellular bacteria that drive the development of Th2/antibody response which in turn suppresses the protective Th1 response, and 2) switch is driven due to loss of the protective Th1 response due to exhaustion/suppression, and concomitant rise in non-protective Th2/antibody response. We investigate the conditions under which these mathematical models give rise to the Th1 to Th2 switch. This approach provides novel insights into the underlying dynamics of the Th1 and Th2 responses during a chronic bacterial infection.

Keywords

*Mycobacterium avium subspecies paratuberculosis*, Johne's disease, mathematical modelling, immune response, Immunology, Population biology.

**Joseph M. Mahaffy**, Department of Mathematical Sciences, San Diego State University, San Diego, CA, USA

## Computer Labs for Calculus in the Life Sciences with WeBWorK

Calculus for the Life Sciences remains a important course for introducing quantitative biology to students in the life sciences. Most schools use classic Calculus tools with some examples drawn from biological examples. Our university has adapted a lecture/computer lab format, where the lectures use a modeling-based approach to learning the material and the computer labs use data-based examples to give hands on modeling experience with real biological examples. Students are introduced to a biological problem, which requires some quantitative tool from Calculus to understand in more detail. A dynamical systems approach is used to better connect students to the biological relevance of the techniques. Examples are chosen from a variety of biological fields, which reinforces the importance of quantitative skills to all students and demonstrates the broad spectrum of applicability of Calculus. Several specifics examples will be presented.

We have developed WeBWorK problems to manage our computer lab exercises (in addition to WeBWorK's use for lecture homework). WeBWorK is an open source, automated homework system supported by the MAA. The automated portion of the computer labs help develop greater accuracy in the students' work and provides immediate feedback to let them know if they are understanding the key concepts. The computer labs have been developed using Excel and some Maple for handling the data analysis. However, the numerical work could easily be handled by software like MatLab. The computer labs include a significant graphing component, primarily in Excel, and some writing. The 2-hour computer lab format of our course gives adequate time for students to learn both the mathematical modeling ideas present in the labs and to develop significant quantitative computer skills. Students acknowledge that the lab skills prove invaluable in their upper division biology classes. Especially because of the power of WeBWorK, we have been able to manage very large classes, which has been important in these times of declining resources to the university.

# Modeling Inter-epidemic Persistence of Rift Valley Fever in Kruger Park's African Buffalo

**Carrie A. Manore**, Tulane University, New Orleans, LA
Brianna Beechler, Oregon State University, Corvallis, OR

Rift Valley fever virus (RVF) is an emerging zoonotic disease that cycles between wildlife, livestock, and people in Africa, causing significant loss. RVF is most often identified in ruminants, both free-living and domestic. It is spread primarily by mosquitoes and, since several mosquito species are competent vectors of RVF, emergence in Europe and North America is a risk. Weather is often considered to be a significant driver of RVF outbreaks via large increases in mosquito populations. Current literature has focused on correlating large epidemics of RVF with El Nino and other weather events. However, little attention has been given to the underlying mechanisms driving the epidemics, such as transmission from mosquitoes to wildlife and the persistence of the virus between wet seasons.

RVF is endemic to Southern Africa, having been first identified in the region in 1951. In Southern Africa, focal or large-scale epidemics occur in a variable temporal cycle of between 7 and 11 years. It is unclear how RVF virus persists during the inter-epidemic periods, but there are two potential nonexclusive explanations for RVF virus persistence: 1) RVF is maintained in the vector population, or 2) RVF circulates undetected in some wildlife reservoir population.

We design and analyze a mathematical model for the dynamics of RVF to address the role of free-living African buffalo (Syncerus caffer) in Kruger National Park in the persistence of RVF. We use data from mosquito trapping and long-term buffalo studies to parameterize and inform the model. We find that a combination of vertical transmission and circulation in an alternate reservoir is the most likely explanation of persistence of RVF in Kruger National Park. This implies that exploration of vertical transmission rates and mosquito dynamics as well as transmission in alternate hosts is needed in order to understand RVF dynamics.

**Deborah C. Markham**, Centre for Mathematical Biology, University of Oxford, United Kingdom
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## Multiscale models of somatic evolution in ductal carcinomas

An important precursor of invasive breast cancer, a leading cause of cancer mortality in women, is ductal carcinoma *in situ*. This is characterized by abnormal proliferation of epithelial cells within the mammary duct without the basement membrane being breached, confining the neoplasm to the duct. Tissue in the duct is not directly vascularized; metabolite exchange occurs with the blood vessels in the stroma surrounding the duct. If cells proliferate abnormally away from the basement membrane, vascular exchange becomes less efficient due to the distance that metabolites must diffuse. Cells that are adapted to these conditions will have a greater chance of survival. Cells within a neoplasm acquire different genetic changes, and thus different phenotypic characteristics. Therefore, a neoplasm can be regarded as being composed of interacting and competing populations of heterogeneous cells. The fitness of a neoplastic cell is determined by its interactions with other nearby cells and with factors in the microenvironment. Thus the development and progression of cancer can be described as somatic evolution.

Previous work has modelled somatic evolution in the mammary duct using a cellular automaton (Gatenby *et al.*, Brit. J. Canc., 2007). In this model, the epithelial cells can become hyperplastic (no longer subject to typical growth constraints thus able to proliferate away from the basement membrane into the ductal space), glycolytic (no longer require oxygen to produce cellular energy, however this has the effect of acidifying the microenvironment), and acid-resistant (able to survive at lower pH than normal cells). The results of this model show that the effects of local metabolite concentrations increase the fitness of neoplastic cells which have acquired all three phenotypic adaptations. Due to their increased fitness, these cells outcompete other cell types present. Moreover, this phenotype has acquired the properties to make it highly invasive. This model has provided a useful initial investigation, however it has a number of limitations. Individual-based models are computationally expensive. This limits the number of cells that can be modelled, and the parameter space which can be explored. Using a continuum model to average over the cell populations would be more computationally and analytically tractable, however there is the risk that the behaviour at the cellular level will be lost.

We are developing continuum models of somatic evolution which will link the cellular and tissue-level behaviour. Most partial different equation (PDE) models of tissue behaviour are phenomenological and a linear diffusion coefficient is chosen. However, PDE representations using non-linear diffusivities often agree more closely with experimental results, and such non-linearities can arise from cellular constraints at the micro-level. Therefore it is essential to develop evidence-based methodologies linking the behaviour at the two scales. The long-term aim of this work is to derive PDE approximations directly from the cellular automaton representation of somatic evolution, thus more accurately representing the microscopic details whilst modelling at the macroscopic level. We will present preliminary results obtained thusfar.

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## AVIAN INFLUENZA: MODELING AND IMPLICATIONS FOR CONTROL

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**Key words:** Avian influenza, shift evolution, reproduction numbers, invasion reproduction numbers, vaccination, culling

At present H5N1 avian influenza is a zoonotic disease where the transmission to humans occurs from infected domestic birds. Since 2003 more than 500 people have been infected and nearly 60% of them have died. If the H5N1 virus becomes efficiently human-to-human transmittable, a pandemic will occur with potentially high mortality. A mathematical model of avian influenza which involves human influenza is introduced to better understand the complex epidemiology of avian influenza and the emergence of a pandemic strain. The model is parameterized based on demographic and epidemiological data on birds and humans. The differential equation system faithfully projects the cumulative number of H5N1 human cases and captures the dynamics of the yearly cases. The model is used to rank the efficacy of the current control measures used to prevent the emergence of a pandemic strain. We find that culling without repopulation and vaccination are the two most efficient control measures each giving 22% decrease in the number of H5N1 infected humans for each 1% change in the parameters. Control measures applied to humans, however, such as wearing protective gear, are not very efficient, giving less than 1% decrease in the number of H5N1 infected humans for each 1% change in the parameters. Furthermore, we find that should a pandemic strain emerge, it will invade, possibly displacing the human influenza virus in circulation at that time. Moreover, higher prevalence levels of human influenza will obstruct the invasion capabilities of the pandemic H5N1 strain. This effect is not very pronounced, as we find that 1% increase in human influenza prevalence will decrease the invasion capabilities of the pandemic strain with 0.006%.

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## Optimal Control of the gypsy moth populations

The gypsy moth, *Lymantria dispar (L.)*, is probably the most destructive forest defoliator in the North America. Gypsy moth outbreaks tend to be spatially synchronized over areas across hundreds of kilometers, which can greatly aggravate the ecological and socioeconomic impacts of high density populations and overwhelm management resources allocated to mitigate impacts. Outbreaks can result in loss of timber and other traditional forestry products. Greater losses tend to occur to the ecosystem services that forests provide, such as wildlife habitat, carbon sequestration, and nutrient cycling. Outbreaks can also change the composition of the community, including indirect changes to native herbivores that gypsy moths tend to outcompete and altering forest succession.

The United States can be divided in three different areas: A generally infested area (where gypsy moth populations are established), an uninfested area (populations are not established), or a transition zone between the two. There are different management programs matching these different areas: (1) Detection/ eradication, which targets new colonies in areas uninfested by the gypsy moth (e.g., the west coast of North America), (2) the Slow-the-Spread program, which consists of a barrier zone along the invasion front in the United States, and (3) suppression of outbreaks in areas that are infested by the gypsy moth as a means to mitigate impacts. This work focuses in optimal control techniques for models of areas where the population is established or in the invasion front.

We design an objective functional to minimize the cost generated by the defoliation caused by the population of gypsy moth and the cost of controlling the population with an aerial spray. The objective was to develop an optimal control framework and perform numerical simulations for various scenarios, that seeks to minimize the total cost due to gypsy moth (damage plus control cost).

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# Quantitative modeling of the terminal differentiation of B cells and mechanisms of lymphomagenesis

Germinal centers (GC) are follicles of B cells that undergo proliferation, differentiation and DNA rearrangement, both through somatic hypermutation and class switch recombination, after presentation of an antigen. GCs are the main sources of memory and plasma cells that produce high-affinity antibodies necessary to protect the body against invading microorganisms. Yet, the mechanisms controlling the molecular switch governing terminal differentiation into either memory or plasma cell are still poorly characterized.

In this work we create a quantitative kinetic model of the transcriptional regulatory module that controls the exit from GCs and the terminal differentiation into plasma cells and memory B cells. Or model recapitulates the dynamics of three key gene regulators of the process, BCL6, IRF4 and BLIMP, and integrates the signals arising from the B cell receptors (BCRs), that sense antibody binding affinity, and de CD40 signaling pathway, that responds to T cell-mediated stimulation. We use gene expression profile data from mature human B cells at several stages of their linage specification to determine appropriate model parameters. Despite a compact structure, the module dynamics are highly complex due to the presence of several feedback loops and self-regulatory interactions, and understanding its dysregulation, frequently associated with lymphomagenesis, requires robust dynamical modeling techniques.

Our model predicts the existence of two different cycles of hysteresis that direct B cells through an irreversible transition towards a differentiated cellular state. Upon stimulation with BCR and the CD40 signaling pathways, B cells experience a transition that leads to a change of state in a bi-stable subsystem, representing a differentiated stage. We show that the interplay between both signaling pathways makes the transition irreversible under normal biological conditions.

Furthermore, by synthetically perturbing the interactions in this network, we can elucidate known mechanism of lymphomagenesis and suggest new candidate tumorigenic alterations, indicating that the model is a valuable quantitative tool to simulate B cell exit from the germinal center under a variety of physiological and pathological conditions.

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## Mathematical Modeling for Cost Analysis of EVELISA-based Johne's Disease Control

Johne's disease (JD) is a chronic granulomatous enteritis of ruminants caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP), an environmental bacterium found in 68% of US dairies tested. The disease is of particular concern to the US dairy industry, resulting in annual economic losses in excess of $220 million. Using a nine-compartment system of difference equations, we modeled the spread of JD on a typical dairy herd, incorporating the use of a test and cull management strategy.

In our model, we included contact structure of dairy cattle with the possibility of adult infections to better simulate JD epidemiology on a dairy farm. In the simulation, cattle that tested as strongly positive were immediately removed from the farm, and calves were not fed with colostrums / milk from those cattle.

The model was used to evaluate the cost-effectiveness of control measures based on a recently developed ethanol vortex enzyme-linked immunosorbent assay (EVELISA). In previous studies, the EVELISA test showed much higher diagnostic sensitivity (97.4%) than that of current ELISA tests (~30%). Versus no testing, use of the EVELISA for JD control resulted in average per capita savings of $82.45 after ten years, which compared favorably with the use of the commercially available ELISA test that saw average per capita savings of only $51.17 after ten years.

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## Atomic Four-Body Statistical Potential for Macromolecular Structure Analysis

Over recent years, exponential growth of the Protein Data Bank (PDB) has facilitated selection of larger, non-redundant subsets of experimentally solved macromolecular structures at higher resolutions, which in turn have provided the data used in developing more effective knowledge-based statistical potentials for improved structure prediction. In contrast to physics-based energy functions, statistical potentials generally perform better and are more computationally efficient at identifying the native structure as a global minimum. Distance-dependent statistical potentials often focus on pairwise atomic contacts within macromolecular structures; however, such energy functions fail to consider important higher-order contributions based on multibody interactions. In the present work, we develop an all-atom four-body statistical potential and illustrate its applicability with a constructive example.

The potential was derived by analyzing coordinate data for 1417 high-resolution ($\leq$ 2.2Å) crystallographic structures selected from the PDB that contain protein chains sharing low (< 30%) sequence identity. Both single-chain and multimeric protein structures are represented in the dataset, the majority of which are also complexed to small molecular or peptide ligands (http://proteins.gmu.edu/automute/tessellatable1417.txt). Coordinates of hydrogen atoms and water molecules were excluded from these files, and a six-letter alphabet (C, N, O, S, M = all metals, X = all other non-metals) was used to designate the remaining heavy atom types in the structures. Atomic coordinates of each structure were supplied to the Qhull implementation of the Delaunay tessellation computational geometry algorithm, which treats the points as vertices and generates an aggregate of non-overlapping irregular tetrahedra. Edges longer than 12Å were removed from every tessellation prior to analysis, so that each remaining tetrahedron objectively identified at its vertices an interacting atomic quadruplet, of which there are 126 distinct possibilities.

An observed relative frequency of occurrence $f_{ijkl}$ was calculated for each atomic quadruplet type ($i$,$j$,$k$,$l$) based upon the proportion of tetrahedra, from among those comprising all the tessellated structures, for which the quadruplet appears at the four vertices. A rate expected by chance was obtained with the multinomial reference distribution

$$p_{ijkl} = \frac{4!}{\prod_{n=1}^{6}(t_n!)} \prod_{n=1}^{6} a_n^{t_n} \text{, where } \sum_{n=1}^{6} a_n = 1 \text{ and } \sum_{n=1}^{6} t_n = 4.$$

In the above formula, $a_n$ represents the proportion of all atoms in the tessellated structures that are of type $n$, and $t_n$ is the number of occurrences of atom type $n$ in the quadruplet. Through application of the inverted Boltzmann principle, the score $s_{ijkl} = \log (f_{ijkl} / p_{ijkl})$ quantified an energy of interaction for the atomic quadruplet. The set of 126 atomic quadruplet types with their respective energy scores defines the four-body potential, which can subsequently be used to compute a topological score for any structure as follows: first tessellate (subject to a 12Å edge-length cutoff), and then sum the scores of the atomic quadruplets identified on the four vertices of all constituent tetrahedra.

As a practical application, we analyzed structures of HIV-1 protease complexed to 140 distinct inhibitors, each with an experimentally known dissociation constant. The four-body potential was used to predict binding energy as the difference between the topological score of the complex and that of the target without the inhibitor (Fig. 1), and a correlation coefficient of $r^2 = 0.64$ was observed between experimental and predicted binding energies (Fig. 2).

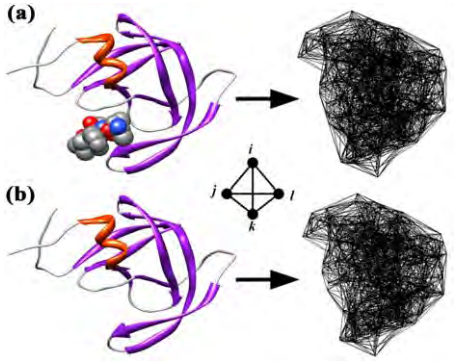


Fig. 1. Atomic Delaunay tessellations of HIV-1 protease.

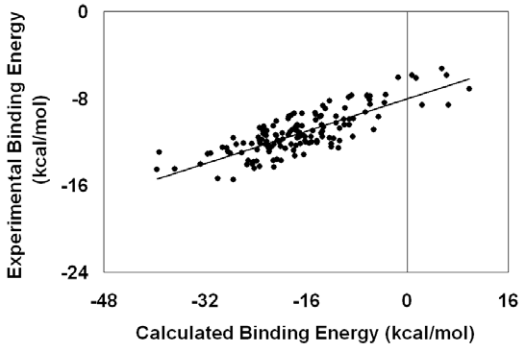


Fig. 2. Scatterplots of HIV-1 protease-inhibitor complexes.

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## A Statistical Analysis of the Impact of Behavior on the Transmission of *Mycobacterium Tuberculosis* Infection and the Development of Drug-Resistant Strains

Tuberculosis (TB) infection has long been established as a disease of poverty, showing increased infection rates, severity of symptoms, and mortality risk in at-risk populations. Alcoholism, drug use, HIV infection, and poverty are well-known contributors to this relationship, though the complexity of the behaviors involved has yet to be fully explored.

This project seeks to create a more detailed profile of the behavioral components of TB spread. Demographic variables, population density and average income, alcohol and drug use, homelessness, and cultural perceptions of diseases and their methods of spread will be analyzed, and particular emphasis will be placed on the factors that impact treatment compliance and the development of drug resistant strains.

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## Modeling Facultative Paedomorphosis in Arizona Tiger Salamanders

The Arizona Tiger Salamanders at the Mexican Cut Nature Preserve in Colorado form a closed population due to the elevation of their habitat. They exhibit facultative paedomorphosis in which salamander larvae either metamorphose into terrestrial adults or become sexually mature while still in their larval form. Although many salamanders exhibit cannibalism of larvae, the Arizona Tiger Salamander also exhibits cannibalism of young by the aquatic adults. We formulate ODE models of this system. We discuss the analysis and interpretation of the models.

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Troy Day, Queen's University, Kingston, ON, Canada

## Is slowing evolution a more effective means of managing antimicrobial resistance than enhancing drug development?

The evolution of drug resistance is a serious impediment to the successful control of many microbial diseases. In principle there are two ways in which this problem might be addressed – (i) enhancing the rate at which new drugs are brought to market, and (ii) slowing the rate at which resistance to currently used drugs evolves. We present a modeling approach based on queueing theory that explores how interventions aimed at these two facets of the problem affect the ability of the entire drug supply system to provide service. Analytical and simulation-based results show that, all else equal, slowing the evolution of drug resistance is more effective at ensuring the adequate availability of effective drugs than is enhancing the rate at which new drugs are brought to market.

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## A Generalized Continuum Model of Tumor Acidity and Invasion

We model the metabolism and behavior of a developing cancer tumor in the context of its microenvironment, with the aim of elucidating the drivers and consequences of altered metabolism—a possible hallmark of malignancy [1] and avenue for novel treatment strategies. Of particular interest is the glycolytic phenotype, a constitutive switch in tumor metabolism of glucose from oxidative phosphorylation to a glycolysis pathway normally reserved for anaerobic conditions [2]. Widely observed across many types of cancer and seemingly paradoxical due to a resulting build-up of toxic acid by-product in the tissue, this phenotype is highly complex and remains incompletely understood.

A potential explanation for the prevalence of the glycolytic phenotype in tumors is the acid-mediated invasion hypothesis [3], which suggests that by acquiring resistance to acidification of the microenvironment, tumor cells expressing the glycolytic phenotype may gain a selective advantage over neighboring healthy cells, functioning similarly to an invasive species in an ecosystem. Many open questions remain concerning the details of this hypothesis and how it fits into the larger features of tumor pH and metabolism, and hence into the somatic evolution of cancer in general. Here, we discuss our efforts to determine how the acid-mediated invasion hypothesis manifests at the tissue level.

We have generalized a canonical non-linear reaction-diffusion model of acid-mediated invasion [4] to consider additional, potentially important, biological features. Numerical methods reveal that our model attains clinically relevant tumor behaviors not captured previously, such as benign growths which lack the ability to invade; and a non-standard asymptotic analysis of the system in a traveling wave framework, inspired by [5], provides an explicit understanding of how fundamental parameters govern the speed and shape of an invading wave of tumor cells. Additionally, comparison with conclusions drawn under the original system—a special case of our generalized system—allows us to comment on the structural stability and predictive power of the modeling framework.

Further study will link this work to a finer-scale consideration of the intricate biochemistry underlying pH regulation in tumors, with the hope of building up a comprehensive picture of tumor acidity and thereby advancing our understanding of cancer metabolism.

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## Measles Vaccine Refusal and its Effects on Communities

Vaccine refusal has become an increasingly prevalent phenomenon in developed countries such as the US and UK. In fact, measles vaccine is reported to be the most frequently refused vaccine by parents in the US, resulting in measles outbreaks various communities,including San Diego in 2008. We investigate the effects of measles vaccination refusal in terms of increased risk of an outbreak and the disease burden.By using an agent-based model built with C++, we simulated the impact of measles vaccine refusal in Alleghany County, Pennsylvania. By varying the levels of the overall vaccine coverage of the children whose parents are skeptical about vaccination,we investigated the risk of an outbreak, the age distribution of the infected individuals, as well as the probability of infection among the vaccinated ones who failed to develop immunity. We concluded that as the years of vaccination refusal increased, the percent risk of infection for the entire community was strongly dependent on the vaccine coverage and that parents and siblings of unvaccinated children were at great risk of infection during an outbreak of measles.

**Christopher Finn McQuaid**, Department of Mathematical Sciences, University of Bath, Bath, UK

## Co-evolution of Resource Trade-offs Driving Nestedness in Host-Parasite Networks

Patterns of nestedness and specialization asymmetry, where specialist species interact mainly with generalists while generalists interact with both generalists and specialists, are often observed in mutualistic and antagonistic bi-partite ecological networks. These have been explained in terms of the relative abundance of the species, using a null model that assigns links in proportion to abundance, but doubts have been raised as to whether this offers a complete explanation. Many other driving factors, such as complementarity, competitive load and defense levels, have been hypothesized. In particular, host-parasite networks offer a variety of examples in which anti-nestedness and the reverse patterns of symmetry are observed.

We propose that the link between parasite specialization and the parasite species-richness of a host may also be driven by resource allocation, which incorporates many of the above ideas. This concerns the co-evolution of hosts and parasites, as hosts allocate resources to optimize defense against different parasites, and parasites to optimize attack on hosts. In a novel approach, this hypothesis is investigated through the adaptive dynamics of a simple ecological system of two hosts and two parasites, in which all species are allowed to evolve the manner in which they trade off their resources between interactions with other species. This alters the force with which a parasite species infects a host, and may be used to compare relative levels of generalization between species.

We show that the co-evolution of these trade-offs in transmissive and defensive traits leads to specialization asymmetry in networks with closely related parasites or faster host mutation rates, but not in networks with more distantly related species. This suggests possible avenues of future investigative work to confirm the causes of nestedness.

**Dr. Shawn A. Means**, Auckland Bioengineering Institute, Auckland, New Zealand

### Mitochondrial Calcium Handling and the Interstitial Cells of Cajal

The Interstitial Cells of Cajal (ICC) generate pacemaking signals controlling contractions of surrounding smooth muscle tissue in the gastrointestinal tract. The mechanism by which they generate these signals is not well known, although calcium (Ca2+) transport between the endoplasmic reticulum (ER) and mitochondria (MT) is shown to be crucial. Precisely how their interaction influences pacemaking signaling is not clear, yet a better understanding of the MT modulation of cytosolic Ca2+ may provide insights into the pacemaking mechanism. We thus aim to extend our previous ICC Ca2+ modeling efforts to include recent experimental data and updated models of MT Ca2+ transporters to facilitate exploration of the ER-MT Ca2+ handling dynamic. Using our own customized unstructured finite element solver written in MATLAB, our resulting spatio-temporal model further studies impact of variant spatial distributions of MT Ca2+ transporters and MT themselves. This study also gives insights into the overall role of MT in modulating cytosolic Ca2+ signals, crucial to behavior of other cellular mechanisms ranging from cardiac cell contraction to neurotransmitter release.

## SMB Plenary Presentation

## Tracking and Curbing the Next Pandemic

**Dr. Lauren Ancel Meyers,** Section of Integrative Biology, Univ. of Texas, Austin

Professor Meyers will discuss global pandemics, why influenza remains a major threat, and how mathematical modeling has been combined with high performance computing to improve disease surveillance, forecasting and intervention.

**Matt J. Michel**, Saint Louis University, St. Louis, MO, USA
Jason H. Knouft, Saint Louis University, St. Louis, MO, USA

## Simulations of phenotype-environment associations and their application to forecasting the adaptability of populations to environmental change

In response to environmental change, a population may: 1) disperse to new areas containing suitable habitat conditions, 2) adapt to the new environment, or 3) suffer population declines and risk local extirpation. While many models have been introduced that examine the new habitat conditions to which a species could disperse in the face of environmental change (e.g., species distribution models), fewer models consider the ability of population to adapt to these changing conditions. Such models are especially critical for species that are dispersal limited.

Species distribution models examine the relationship between species occupancy and environmental variables and then use this relationship to determine areas which contain suitable environmental conditions to which species can disperse. We extend this framework to predict the ability of populations to adapt to environmental change by examining the relationship between phenotype and environment. These phenotype-environment associations are then used to determine the phenotypes the population must attain in order to persist within a habitat with altered environmental conditions.

First, we conduct simulations using a quantitative genetics model of linear reaction norms to examine the effects of natural selection, phenotypic plasticity, and temporal autocorrelation in the environment on the strength of phenotype-environment associations. Our results demonstrate that phenotype-environment associations are promoted by strong natural selection, high magnitudes of plasticity, and greater degrees of positive temporal autocorrelation (i.e., when the environment in the current generation is similar to the environment in the previous generation).

Second, we apply this framework to examine the adaptability of stream fish populations to future changes in flow rates caused by global climate change. Our analysis indicates that fish body shape was significantly associated with contemporary flow, as individuals found in high-flow habitats have a more streamlined body shape than individuals from low-flow habitats. Hydrologic models based on future temperature and precipitation data from regional climate models predict subbasin-level declines in flow rate in the years 2051 – 2060 relative to current flow rates. Thus, stream fish would require less-streamlined body shapes in the future. Using the same simulation models as above, we determine the combinations of selection intensity and phenotypic plasticity necessary for each population to reach the expected body shape. Our analysis reveals that the adaptability of some populations to future changes in flow rate requires strong and potentially unrealistic levels of selection and plasticity. Consequently, species may incur substantial demographic costs across populations.

## Highs and Lows of an Interdepartmental Undergraduate MathBio Program

**Jason E. Miller**, Ph.D.
Dept of Mathematics, Truman State University, Kirksville, MO

**Abstract**: With the publication of Bio 2010, many felt that adapting undergraduate curricula to accommodate that report's recommendations would yield easy fruits. Faculty at Truman State University energetically pursued external funding that allowed them to establish a research-focused training program in mathematical biology. The program used the University's residential nature to build a year-round community of talented undergraduates and creative faculty. They 'build' products that result in presentations (poster and oral) at professional meetings and publications in peer-reviewed journals. The program also motivates students to pursue interdisciplinary graduate degree programs and related positions in industry.

However, the founders of the program have not seen it bear easy fruits. Students don't recruit themselves to the program. This talk will outline the challenges faced by Truman's efforts to create and sustain an interdisciplinary program in mathematical biology. It will also sketch the ways it has inspired other departments to pursue interdisciplinary opportunities in STEM and STEM talent expansion efforts.

**Christopher Mitchell**, University of Texas at Arlington, Arlington, TX, USA
Lindsey Dornberger, University of Texas at Arlington, Arlington, TX, USA
Brian Hull, University of Texas at Arlington, Arlington, TX, USA
Wilber Ventura, University of Texas at Arlington, Arlington, TX, USA
Haley Shopp, University of Texas at Arlington, Arlington, TX, USA

## Death of the Bees: A Mathematical Model of Colony Collapse Disorder in *Apis mellifera*

A mysterious problem has developed within honey bee populations; in a worst case scenario, bee hives will spontaneously collapse as the entire population disappears from the hive. This phenomenon has been named Colony Collapse Disorder (CCD). The problem is recent and has no known cause, though it is surmised to stem from one or multiple infections. In order to gain insight into its dynamics and possible causes, we have attempted to create a mathematical model. First, we establish a baseline model for the population dynamics of a single healthy hive, using a system of ordinary differential equations. To this model we then add equations which account for the disease affecting the population. Here we must take some liberties regarding assumptions of the disease source given how little is known about CCD, but our model accommodates both direct (bee-to-bee) and indirect (via contaminated plants as vectors) transmission. An analysis of the model's six equilibria including disease-free, endemic, and extinction states develops criteria for distinguishing among several scenarios, including both survival and extinction due to CCD. These criteria identify several key parameters which could offer insight into the nature of the cause of this colony collapse. All theoretical results are supported by a set of numerical simulations and are consistent with raw data regarding the dynamics of the disorder.

This research is part of an undergraduate training program, Undergraduate Training in Theoretical Ecology and Epidemiology Research (UTTER), at UT Arlington supported by an NSF UBM-Institutional grant (no. DUE 0827136 )

**Julie Mitchell**, University of Wisconsin – Madison, Madison, WI, USA
Omar Demerdash, University of Wisconsin – Madison, Madison, WI, USA
Xiao-lei Zhu, University of Wisconsin – Madison, Madison, WI USA
Michael Daily, University of Wisconsin – Madison, Madison, WI, USA

# Knowledge-Based Structural Approaches for Predicting Hot Spots of Protein Binding and Allostery

Using information derived from protein structures, it is possible to predict amino acid positions where mutations will have a deleterious effect on protein binding or allosteric communication. The KFC2 model captures 80% of alanine scanning mutagenesis hot spots, which result in a binding energy increase of at least 2 kcal/mol. A unique feature of the model is a local plasticity feature that suggests whether a change in sequence can be accommodated through local sidechain rearrangements. A different plasticity measure, known as local structural entropy, is a dominant feature in our AlloSIND model for allosteric hot spots that lie between the effector and active sites of allosteric proteins. One possible interpretation is that rigidity of internal protein secondary structure prevents an allosteric protein from absorbing the impact of effector binding locally, resulting in longer range conformation effects.

**Gabriel Mitchell**, School of Biology, Georgia Institute of Technology, Atlanta, GA, USA
Joshua Weitz, School of Biology and School of Physics, Georgia Institute of Technology, Atlanta, GA, USA

## A Statistical Analysis of Ecosystem Stability from Local and Global Interaction Structure

The relationship between community stability and community interaction structure is of historical and ongoing interest in ecology. In the 1970s, Robert May and others investigated this relationship by analyzing statistically how the average connectance of random community matrices affects the largest eigenvalue of the Jacobian at the interior fixed point, which determines the stability of the community. In doing so, they were able to establish a statistical relationship between stability and a particular global measure of the community's interaction structure (average connectance). At the crux of their analysis was the assumption that the matrices in their ensemble have elements drawn from independent distributions. However, many random matrix ensembles of ecological interest will have elements that are highly correlated with one another, which violates the independence assumption. In this scenario the average connectance no longer characterizes the stability properties of the system. Nevertheless, there is evidence that higher order measures of interaction structure like nestedness or modularity do correlate with the stability of the system. The mechanisms by which the correlation arises and the conditions under which this pattern occurs have yet to be elucidated. Our goal is to extend the classical work of May to determine the relationship between stability and higher order measures of interaction structure that take into account correlations between interactions. Identifying these mechanisms and determining under what conditions they exist should prove useful in reasoning about the significance of patterns of nestedness or modularity observed in natural communities.

In this work, we make an explicit connection between the stability of Lotka-Volterra systems and network metrics of interest through a structured mean field theory. Our mean field approach allows us to reason about the effects of both the global interaction structure (as seen through the fictitious mean species) and the local interaction structure (as seen by a particular species under the mean field approximation). By distinguishing between local and global contributions to network metrics and their effect on stability we can understand, for example, how removal of species with small or large contributions to nestedness affects the asymptotic composition of communities (e.g. through extinction events or gross changes in abundance). In addition to making an explicit connection between stability and networks metrics, we can also examine the indirect connection between these metrics and other aggregate measures of the ecosystem such as total population abundance, productivity and the like.

Finally, we pay special attention to a class of competitive Lotka-Volterra systems with parameterized community matrices, where the parameter controls the strength of interspecific competition. In the limit of weak interspecific competition, there is a single interior fixed point that is also a global attractor. In the limit of strong interspecific competition the eigenvalues of the community matrix itself will tend to determine the stability of the system, as noted in the classical work of May on random competition. In the intermediate regime the stability of interior and boundary fixed points is non-trivial. Nevertheless we can apply our mean field approach in this regime, and so offer insight into the statistical behavior of competitive Lotka-Volterra systems as a function of the relative level of interspecific competition.

## Agent-based Modeling of Wound Healing

**Qi Mi, Ph.D**
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Agent-based modeling (ABM) has recently emerged as an innovative computational approach to the simulation of complex biological systems and an alternative to traditional ODE or PDE based methodology. The entities (agents) in the ABMs can represent molecules, cells, or higher order cellular structures. It is relatively easy to transfer biological interactions into rules that define the explicit actions of the agents. The ABMs are especially useful for generating hypotheses and investigating spatially and temporally heterogeneous patterns of the biological system. In my talk, I will present my studies of using agent-based approach to model the wound healing in the settings of diabetic foot ulcer and epithelial cell layer migration. A multi-scale ABM framework-SPARK which has been recently developed in our group will also be discussed.

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## Arrow Diagrams Arising from a Synthetic Biology Investigation

We are working with biology students on our campus and collaborating with mathematicians and biologists at Davidson College as part of an NSF-funded synthetic biology research team. One project undertaken by the team is the design and construction of a method to optimize a metabolic pathway in *E. coli*. In our initial study of how to search a space for an optimal result, we developed the concept of *arrow diagrams*, a directed graph subject to multiple constraints, and have investigated if such diagrams can be labeled under certain conditions. In addition to their potential impact on the order of our lab experiments, these graphs have interesting combinatorial properties.

**Yoichiro Mori**
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## Pump-Leak Models of Cell Volume and Electrolyte Control

Homeostatic control of cell volume and intracellular electrolyte content is a fundamental problem in physiology and is central to the functioning of epithelial systems. These physiological processes are typically modeled using pump-leak models, a system of differential algebraic equations that describes the balance of ions and water flowing across the cell membrane. Despite their widespread use, very little is known about their mathematical properties. In this talk, we present recently established analytical results on the existence and stability of steady states for a general class of pump-leak models. We treat two cases. When the ion channel currents have a linear current-voltage relationship, we show that the there is at most one steady state, and that the steady state is always asymptotically stable. When minimal assumptions are placed on the properties of ion channel currents, we show that there is an asymptotically stable steady state so long as the pump current is not too large. The key tool in our argument is a free energy relation satisfied by a general class of pump-leak models, which can be used as a Lyapunov function to study stability. It time permits, we will discuss spatial generalizations of the pump-leak models and present some preliminary applications of the model.

**Anna Mummert**, Marshall University, Huntington, WV, USA

## Studying the Recovery Algorithm for the Time-dependent Transmission Rate(s) in Epidemic Models

While the recovery rate of a disease can be measured in a controlled laboratory setting and these values used to estimate the value during the actual disease outbreak, the same is not true for the transmission rate. The transmission rate is known to be difficult to measure due to its dependence on the probability of transmission between individuals and social contact rates. On the other hand, there is a wealth of information that could be extracted regarding disease transmission and recovery if the time-dependent transmission function were known. For example, it would be possible to test hypotheses such as whether the school year causes increased disease incidence due to increased contacts among children.

Determining the time-dependent transmission function that exactly reproduces disease incidence data can yield useful information about disease outbreaks, including a range potential values for the recovery rate of the disease and could offer a method to test the "school year" hypothesis (seasonality) for disease transmission. Recently two procedures have been developed to recover the time-dependent transmission function, $\beta(t)$, for classical disease models given the disease incidence data. These two procedures to recover $\beta(t)$ can be extended to a broad class of *SIR*-type compartment models, including the *SIR* model with waning immunity, the *SIR* model with a time-dependent indirect transmission rate, to the discrete time setting, the stochastic setting, and assuming an specific exit distribution from the infected class.

We first review the $\beta(t)$ recovery procedures and give the resulting formulas, using both methods, for the susceptible-infected-recovered (*SIR*) and susceptible-exposed-infected-recovered (*SEIR*) models. Using a modification of one procedure, the two formulas are shown to be identical. Second, we explore several technical issues that appear when implementing the procedure for the *SIR* model; these are important when generating the time-dependent transmission function for real-world disease data. Third, we extend the recovery method to heterogeneous populations modeled with a certain *SIR*-type model with multiple time-dependent transmission functions.

We demonstrate the $\beta(t)$ recovery procedure for two population classes assuming that the length of the disease outbreak is short compared with the time required to "grow up" from the child class into the adult class. Thus there is no movement from one class to another. With two classes, there is a possibility of four different transmission rates within and between the two groups, and two different recovery rates.

For two populations, we assume that the incidence data functions, $I_1(t)$ and $I_2(t)$, are known, allowing us to solve for two transmission functions. If additional information is known about the disease spread then it may be possible to solve for the four transmission functions completely.

We consider two possible scenarios resulting in two distinct transmission functions. First, we assume that the disease spread is different between adults and among the two classes than among the children only. Second, we consider the scenario when the transmission matrix is separable (has proportionate mixing), where the number of contacts between individuals in two different groups is assumed to be proportional to the activity levels and sizes of the groups. In particular, the "infectivities" of each group are the same and only the "susceptibilities" of the groups are different.

We apply the $\beta(t)$ recovery procedure to data from the 2002–2003 influenza season and for the six seasons from 2002–2003 through 2007–2008, for both one population class and for two age classes. We discuss the consequences of the technical conditions of the procedure applied to the influenza data. We show that the method is robust in the heterogeneous cases, producing comparable results under the two different hypotheses. We perform a frequency analysis, which shows a dominant 1-year period for the multi-year influenza transmission function(s).

**Mary Myerscough**, David Khoury, School of Mathematics and Statistics, University of Sydney, NSW, Australia
Andrew Barron, Department of Biology, Macquarie University, NSW, Australia

## Honeybee demography: the effects of food and brood.

In honey bee colonies, which are known as hives, adult worker bees can be divided into two broad castes: hive bees and foragers. Foragers work outside the hive, collecting nectar and pollen while hive bees work inside the hive, caring for brood, cleaning, and storing what the foragers have collected. Brood is the collective name for the eggs, larvae and pupae that develop into adult bees. When worker bees first emerge from pupation they work as hive bees and make the transition to foragers as they age. The age of the worker bees at this transition is affected by the number of existing foragers and the levels of stored food in the hive.
A crucial contributer to hive well-being is the health, productivity and longevity of its foragers. When forager numbers are depleted there is a significant effect, not only on the amount of nectar and pollen that can be collected but also on the colony's capacity to raise brood and on the age that bees make the transition from hive bee to forager. We use a set of differential equation models to explore the effect on the hive of high forager death rates on the total population of the hive and the effect of precocious transition to foraging on food collection, brood rearing and hive viability.

Holly D. Gaff, Old Dominion University, Norfolk, VA, USA
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## Quantitative Vector Ecology: Modeling Tick-Borne Disease Risk in an Ecological Context

Vector-borne diseases are complicated because in addition to their impacts on human health, the pathogens responsible for disease are often dependent on complex enzootic cycles that may include many animal species and have specific environmental conditions. Tick-borne illnesses such as Rocky Mountain spotted fever (*Rickettsia rickettsii*), Tidewater spotted fever (*Rickettsia parkeri*), and Lyme disease (*Borrelia burgdorferi*), have significant public health implications, but the dynamics of these diseases cannot be understood or modeled without an understanding of the underlying ecology of the ticks and their hosts. Here we discuss the findings of our long-term field collection effort that brings together information on tick species, tick abundance, disease prevalence, and host and habitat preference over four years in the southeastern United States. Using our field data, we have created an agent-based model using Netlogo software. This model is designed to explore the dynamics of Gulf Coast ticks (*Amblyomma maculatum*) and prevalence of Tidewater Spotted Fever as these ticks are introduced into new geographic areas. We will compare the results of our model with discovery of a newly established population of Gulf Coast ticks, and we will discuss the proposed expansion of our model to include successional dynamics and additional tick and pathogen species.

**Toshiyuki Namba** and Atushi Ibuki, Osaka Prefecture University, Sakai, Osaka, JAPAN

## Effects of Apex Consumers Cascade Dynamically across Trophic Levels

In recent decades, it has been hypothesized that the loss of large apex consumers may exert pervasive influence on nature, and the idea that an ecosystem is shaped by the top-down effects is now widely accepted.

Simple ecosystems in the northern Pacific Ocean are particularly suitable to test the hypothesis. In 1970's, communities at islands lacking sea otters were characterized by high density of sea urchins and a distinct lack of macrophytic vegetation.. In contrast, communities at islands with sea otters had relatively high kelp densities and low sea urchin biomass (Estes and Palsamino 1974). However, in 1990's, sea otter populations declined unexpectedly over large areas and the increased killer whale predation was supposed to be the likely cause of these declines (Estes et al. 1998).

In this talk, we propose simple mathematical models of the communities without or with sea otters, and those with killer whales. We will show that competition between kelps and coralline algae in the basal trophic level strongly affects community dynamics and causes violent oscillations which lead to imminent extirpation of the kelp population. However, introduction of the sea otters suppresses not only the sea urchin population but also the violent oscillations in communities with the sea urchin as an apex consumer. Thus, in this model, no population oscillations appear in communities at islands inhabited by sea otters, although the coralline algae may become extinct. Finally, top-down effects of the killer whales cascade down to the kelp population through the sea otters and sea urchins and save the coralline algae from extinction. However, strong top-down effects of the killer whales destabilize the community and release the violent oscillations that were suppressed by top-down effects of the sea otters. Thus, the trophic cascades have not only static but also dynamic effects on food chains and the effects are totally different depending on the number of trophic levels.

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# Optimal management controls for maximizing the recovery of an endangered fish species

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**Abstract**: A computationally-expensive individual-based model (IBM) was used to simulate the population decline of delta smelt during 1995 to 2005 in the Upper San Francisco Estuary. We approximated the IBM's output with a spatially-explicit matrix projection model. By applying optimal control theory to the matrix model, we determined cost-effective management actions involving redirected movement and improved habitat (affecting mortality and growth) that would maximize long-term population growth during this period of decline.

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## Mosquito demography and nourishment habits can account for observed patterns in malaria transmission

A deterministic SEIRS model for malaria that accounts for mosquito demography and nourishment habits is developed and studied. The model differs from classical SEIRS malaria models in that the mosquito population involved in disease transmission is identified and well-accounted for. We show that the model can exhibit disease-free and endemic equilibrium solutions and investigate whether naturally occuring fluctuations and oscillations that characterize the mosquito population dynamics can drive the full model system to oscillate over time, thereby accounting for observed patterns in malaria prevalence. A sensitivity analysis is carried out to identify important parameters of the model. The possibility of a backward bifurcation, a phenomenon that is essential in designing control strategies is explored, and various malaria control strategies are examined through two threshold parameters, one associated with mosquito dynamics and the other associated with disease dynamics.

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## Reaction-Diffusion Models of Compartmentalization of Steroid Synthesis

Steroidogenic enzymes can be compartmentalized at different levels, some by virtue of being membrane bound in specific intra-cellular compartments. Although both 3β-hydroxysteroid dehydrogenase/$\Delta^5$-$\Delta^4$ isomerase (3β-HSD) and 17α-hydroxylase/17,20-lyase cytochrome P450 (P450c17) are expressed in the endoplasmic reticulum (ER) membrane, these proteins may still be spatially separated within this membrane system. Side chain cleavage cytochrome P450 (P450scc) is anchored to the inner mitochondrial membrane and this organelle is the major source of pregnenolone feeding steroidogenesis. Furthermore, steroidogenic enzymes can also be partitioned in different cells. Although well recognized, the effect of enzyme compartmentalization on the rate of steroid synthesis and the balance of different steroids is unclear. This study uses mathematical modelling to investigate the effect of enzyme compartmentalization on steroid synthesis in a human-ovine-bovine model of steroid synthesis. Three levels of enzyme compartmentalization examined are: 1) the spatial separation of the enzymes within the ER; 2) the enzyme compartmentalization into different organelles of a cell, and 3) the enzyme partitioning into different cells.

Steroids are small molecules that have a high intracellular diffusion coefficient, hence it is expected that the spatial separation in the ER and the compartmentalization in a cell of steroidogenic enzymes has minimal effect on steroid synthesis (1). To test this, a reaction-diffusion model of the network of reactions catalyzed by P450c17 and 3β-HSD is developed. Simulations are run with a proposed enzyme distribution within the ER and the cell. The results of the model with these spatial configurations are compared to that of the non-compartmentalized model which did not consider any spatial distribution of enzymes (1).

To study the effect of partitioning into different cells of the enzymes required for oestrogen synthesis, an extended reaction-diffusion model is developed that also includes the aromatisation of androstenedione to oestrone catalyzed by P450arom. Two models of organisation of the cells containing different enzymes are examined: two-cell and two-layer-of-cell models. The results of simulations with three different scenarios of enzyme partitioning in each model are compared. This is to test the hypothesis that tissue-specific partitioning of steroidogenic enzymes could be an important regulator of steroid synthesis.

Model simulations show that the spatial separation of steroidogenic enzymes within the ER has a minimal effect on steroid synthesis. The compartmentalization of the enzymes into different organelles of a cell creates small cellular steroid gradients. The partitioning of steroidogenic enzymes in different cells reduces the rate of steroid synthesis. The greater is the distance between the cells that contain different enzymes the more the rate of steroid synthesis is reduced. Additionally, when 3β-HSD is not in the same cell with P450scc and P450c17, the enzyme become less competitive than P450c17 for their common substrates, hence the balance of $\Delta^5$-pathway product (oestrone) to $\Delta^4$-pathway product (17α-hydroxy-progesterone) is favoured. It is also proved that neither the enzyme compartmentalization within a cell nor the enzyme partitioning into different cells alter the qualitative behaviours of steroid synthesis in response to variation in enzyme activity or the rate of P5 supply, as shown in the non-compartmentalized model (1).

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## Modeling the Spread of White-Nose Syndrome, an Emerging Disease of Bats

During the first several years of the White-Nose Syndrome (WNS) epizootic affecting hibernating bats in North America, it and its causative pathogenic fungus *Geomyces destructans* (Gd) exhibited high rates of dispersal averaging about 600 km/year and high virulence with colony mortality frequently exceeding 95%. However, in recent years, regional differences in the spread of the disease and survival of hibernating bats are evidenced in northern versus southern latitudes. Also, it is thus far limited to the eastern half of the United States and Canada. To help understand these differences in WNS dispersal in the United States, and to determine if spread will continue nationwide, we project the spread of the fungus at national, regional, state and local scales by using an agent-based, spatially-explicit, temperature-dependent, dynamic stochastic model developed over two summers.

For nationwide, high-resolution results, serial computation was inadequate to produce the detailed results we required in a reasonable amount of time. The WNS dispersal model began as a student project written in Visual C#. We initially redesigned it into a multi-core computation engine driven by python scripts on an eight-core Mac Pro for regional results, then later a C++, OpenMP model executed on Kraken (kraken.nics.tennessee.edu) for nationwide results. Kraken is a petaflop scale, Cray supercomputer maintained by the University of Tennessee for academic use. Our runs required 18K hours of compute time on Kraken.

For regional and national simulations, we approximate cave locations by county centroid in the contiguous U. S. and utilize karst cave density to determine habitability. The ambient surface temperature of each county centroid is used as a proxy for this cave's temperature. The results of several thousand simulations are summarized to determine robust trends and visualized in Google Earth.

The disease dispersal structure demonstrates regional scale movement towards epicenters followed by local disease expansion around the epicenters. Simulations suggest several robust hypotheses relating to survival at the national level: 1) Warmer temperatures provide a refuge for WNS-susceptible bats in the southern U.S.; 2) There is a spatial bottleneck that could present feasible opportunities to control or delay the western spread of WNS; and 3) The disease is slowed by the Great Plains and Rocky Mountains, but projects to continue to spread into the western U.S.

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## Changing The Landscape - Can We Use Drugs To Steer Evolution Away From Resistant Phenotypes?

Multidrug treatments are becoming more important as resistance to antibiotics and cancer treatment increases. We explore the possibility of multidrug treatments in which drugs are administered sequentially. The aim is to use a first drug to drive the evolution of a pathogen to a certain point in the fitness landscape from which there is no mutational path to a genotype of peak fitness in the landscape of the second drug. In other words, we aim to exploit resistance to one drug to enhance the effectiveness of a second.

A number of earlier studies have shown that certain trajectories within a fitness landscape may be inaccessible. For example, a peak fitness may be inaccessible from a given genotype if that genotype is a local optimum. In randomly generated landscapes of N alleles with 2 states the expected number of local optima is 2^N / (N+1) and the average length of an evolutionary walk is log(N+1). This suggests evolution in these landscapes need not each a global optimum of fitness.

However it has been shown that an adaptation in a given environment which decreases fitness in a second may later be reversed in the second. This suggests that the fitness landscapes of drugs used in combination must correlate in a very specific way else the evolution in response to the first maybe be undone when the second rug is applied. Whilst previous research has focussed mainly on evolution in bacterial pathogens we believe the concepts are highly generalizable and applicable to cancer cells too. As such we consider fitness landscapes in an abstract setting.

We consider paths of mutation with respect to a pair of landscapes, calling a mutation path from one genotype to another reversible if it can be traversed by single-gene fitness-increasing mutations in one landscape and traversed in the reverse direction in the second landscape.

We experiment with fitness landscapes generated by the NK model and analyse the topology of such landscapes in pairs to count paths which are reversible. This gives a notion of correlation between landscapes: two landscapes are considered correlated if they have a low number of reversible paths between them. We show that a high correlation is essential to finding drugs suitable for sequential use. Further we consider the effect of the ruggedness of landscapes on correlation and find a high degree of ruggedness alone is not sufficient to generate highly correlated landscapes.

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## A Spatially Explicit Analogue of Charnov's Marginal Value Theorem

Charnov's Marginal Value Theorem describes the maximally efficient way for a foraging animal to harvest patchily distributed resources. The predictions of this theorem provide a useful benchmark against which to measure real-world foragers. Departures from these predictions imply that an animal is foraging sub-optimally, and hence that other factors must be influencing its behavior. Charnov's theorem has several important limitations: it does not explicitly model the spatial distribution of resources, it assumes that patches have well-defined boundaries, and it represents resource harvesting as a deterministic and continuous process. In reality, foragers often encounter resources stochastically as discrete events, and the spatial configuration of these resources can have important consequences. In this work, we use random search theory to construct a spatially explicit optimal foraging model. The predictions of this new model provide a benchmark for assessing foraging performance. This model makes very basic assumptions about the forager's perceptual and cognitive abilities, and hence maintains much of the simplicity and generality that make Charnov's theorem appealing. Unlike Charnov's theorem, it directly incorporates the spatial components of foraging behavior. We argue that it represents the most natural spatial extension of Charnov's theorem.

Our benchmark model determines when an optimal forager should switch between extensive and intensive search behavior, analogous to the way that Charnov's theorem determines when a forager should switch from harvesting a patch to leaving it. We examine how resource distribution affects these analytic predictions about optimal search behavior. We also simulate commonly invoked hypothetical foraging strategies, such as Lévy walks and intermittent searches based on giving-up times, and compare the efficiencies of these strategies with that of our benchmark model. Our findings emphasize the importance of resource distribution in assessing foraging efficiency.

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## Understanding Blood Pressure Regulation through Mathematical Modeling

Understanding the cardiovascular control system is crucial for gaining perspective on the physiology of a healthy individual as well as in detecting abnormalities. In recent years the modeling of various aspects of the cardiovascular system has been especially insightful. In particular, heart rate models reveal underlying mechanisms of blood pressure regulation. The baroreflex has been identified as an important contributor to the short-term blood pressure control mechanism. This is a negative feedback system that aims to maintain a constant range for blood pressure. It involves specialized neurons, called baroreceptors, which are stretch sensors that respond to arterial pressure and are predominantly located in the aortic arch and carotid sinus.

Throughout the years, various mathematical models have been developed which quantify the pressure-response relationship. Recently a unified model has been proposed that reflects all the known characteristics of baroreceptor response including: saturation, threshold, adaptation, post-excitatory depression and sensitivity to the rate of change of pressure. We demonstrate how parameters of the model are altered due to conditions that affect baroreceptors such as aging or hypertension. Further we augment the baroreceptor model to include the description of the sympathetic and parasympathetic outflow to predict the heart rate.

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## Symmetries, conservation laws, Lagrangians and ... quantization of biological systems?

In a very interesting recent review to honor the 50th Anniversary Year of the Journal of Theoretical Biology one reads: *It is frequently claimed that like Newton's invention of calculus biological theory will require 'new mathematics'.... There are, however, many areas of mathematics that have been neglected by theoretical biology that could prove to be of great value. Einstein's work on general relativity, for instance, made good use of mathematical ideas, in particular differential geometry that had previously been developed with completely different motivation. More likely than not, the formal structures have been set forth in some context, and await their discovery and subsequent development in representing biological theory* [1].
Since many mathematical tools used in Physics have also been used in biology with alternate success, we present a somewhat forgotten and neglected tool, a tool that in one of its outcomes, Noether symmetries, helped Einstein and Klein in their quarrel with Hilbert about the energy-momentum conservation of general relativity theory [2]. This tool is Lie continuous symmetries, that yield conservation laws, calculus of variation setting, and ultimately quantization.
The application of Lie symmetries to various biological models have already been shown to either provide more accurate predictions [3] or implement [4], [5], [6] the usual techniques related to qualitative and numerical analysis, that are common tools for any mathematical biologist.
We would like to stir up some controversy with the purpose of making both mathematicians and biologists pondering over some missed opportunities [7].
Since a good example is the best sermon, classical known mathematical models such as the Volterra-Verhulst-Pearl equation [8], [9] shall be used to show the many symmetries and conservation laws they possess, the many Lagrangians and therefore different variational problems they admit [10], and finally the quantization (through Schrödinger equation) that they lead to.

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1

## Optimal Control Applied to Immuno-epidemiological Models

An immuno-epidemiological model is formulated and analyzed to show that we have a well-posed model comprising a "within-host" system of ordinary differential equations (ODEs) with a "between-host" system of partial differential equations and ODEs. Stability results for the model are investigated. Using a representation from the method of characteristics and a fixed point argument, we prove the existence and uniqueness of a solution to our system. An optimal control problem for the immuno-epidemiological model is considered. This work is in collaboration with Suzanne Lenhart, Maia Martcheva and Souvik Bhattacharya.

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## Applying Heuristic Algorithms to Optimization Problems Concerning Agent-Based Models

The applications of agent-based modeling for studying complex systems are wide-ranging. Mathematical techniques for analysis of these complicated systems help formalize the study of agent-based models (ABMs) by placing them in a more rigorous context. When possible, conversion of ABMs into discrete mathematical models enhances the potential for statistical and mathematical analysis. Global dynamics can be described by a system of difference equations, precluding the need for simulation. Such equations are derived from the rules that govern an ABM. Given that ABMs are often designed in order to investigate natural systems, the development of optimal control theory is critical for successful analysis.

Given the simultaneous update scheme used in most agent-based models, difference equations provide a natural framework for translation of ABMs. One equation is obtained for each category of agent and patch; the equations may represent populations, densities, locations, and so on. Translation is described for a spatially heterogeneous model known as SugarScape. In this model, different regions of the landscape contain different levels of sugar (distributed as a gradient), and abstract agents traverse the landscape in an attempt to accumulate as much sugar as possible. Agents have different vision and metabolism: higher vision allows an agent to more easily move to sugar-rich regions, but a higher metabolism means an agent burns sugar stores at a higher rate. Taxes are periodically collected from the agents, with tax rates based on an agents vision, metabolism, and location. An optimization problem is posed: given that higher taxes lead to a higher likelihood of death, what is the best tax structure in order to maximize tax income and minimize the number of deaths? The search for the answer to this question is conducted using difference equations, with heuristic algorithms as the search method.

Solutions obtained from heuristic methods are confirmed via simulation. Heuristic algorithms used include a genetic algorithm, simulated annealing, and random-mutation hill-climbing. Because such methods cannot be guaranteed to converge to a global optimum, results are compared to those obtained via random search. In all cases, the heuristic algorithms significantly outperform simple random searches. The translation of ABMs to formal mathematical models precludes simulation and thus results are obtained that are more reliable and require only seconds to compute.

While a standardized translation protocol for ABMs to discrete mathematical models is still lacking, this example demonstrates several advantages of using difference equations for analysis of agent-based models. Optimal control results can be applied directly to the models or to the obtained discrete math models, allowing for a more rigorous analysis of ABM dynamics. Given that ABMs are used in many areas of interdisciplinary research, application and development of a mathematical framework for such models allows more and better results to be attained, further enhancing the potential for ABMs to inform and guide future scientific study.

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## The AC-DC motif – a circuit which allows cells to respond to morphogen signaling in the vertebrate neural tube

During the course of embryonic development, an initially homogeneous population of cells organizes into an exquisitely patterned organism, consisting of multiple cell types. How the information encoded in the DNA is interpreted to create this three-dimensional pattern of cell types has intrigued scientists for many years. One strategy for specifying cellular differentiation is the local production and subsequent diffusion of a "morphogen." The signal conferred to cells varies in space and is used by them to decide their fates.

An example morphogen is Sonic Hedgehog, which, in vertebrates, specifies neural progenitor domains. These later develop into different types of neuron. We present a mathematical model of the gene regulatory circuit that interprets the Sonic Hedghog signal at the cellular level. We show that the circuit responds to both the level and duration of the signal and confers properties of hysteresis and robustness on cells. We show that, in addition to switch-like behavior, the circuit can also exhibit oscillations. We therefore term the circuit the "AC-DC motif."

We suggest that through changes in for example a binding affinity, the AC-DC motif could have been re-used during the course of evolution for either switch-like or oscillatory functions, both of which are important in embryonic patterning.

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## Mathematical Modeling of Multi-Species Motor-Cargo Transport

Intracellular transport of cargo, including macromolecules, vesicles and organelles, through the attachment to microtubules via molecular motors, such as kinesin and dynein, is a complex process that plays a significant role in neuronal function. Disruption of this transport has been linked to neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases. Thus, studying the interactions among different types of cargo and molecular motors can lead to a better understanding of the complicated processes involved during intracellular transport.

Here, we will present a mathematical model based on traffic-like partial differential equations to describe coupled motor-cargo transport within the squid giant axon when two different types of cargo are present, competing for motors. Using parameters in the mathematical model that can be directly obtained from experimental measurements within the squid giant axon allows for predictions of the behavior of the cargo to be compared to and validated with experimental outcomes. When there is an excess of motors present, an analytical solution of the governing equations can be obtained, and in the long time limit agrees with the experimental results. However, when motors are scarce, the cargo transport is nonlinearly coupled. As a first step towards understanding this phenomenon, we analyze experiments in which the C-terminus of amyloid precursor protein (APP-C) is co-injected with APP-C coated nano-beads in the squid giant axon leading to competition for motors.

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## Sources and scales of heterogeneous mosquito-borne pathogen transmission

Mosquito-borne diseases pose tremendous public health challenges in a variety of ecological and epidemiological contexts throughout the world. Efforts to control mosquitoes and the pathogens that cause these diseases have relied heavily on insights from mathematical modeling. In particular, the seminal work by Ross and Macdonald completed around 1970 has had a tremendous and lasting influence on research and policy since then. Nonetheless, predictions based on the Ross-Macdonald model often clash with real-world observations, largely because the model ignores empirically well-supported heterogeneities in transmission. To reconcile these deficiencies in existing theory, we develop a new model focused on the ecological and epidemiological context of encounters between mosquitoes and vertebrate hosts. This model features discrete, spatially referenced sets of locations for larval mosquito development and separate locations for mosquito blood feeding on hosts. It accounts for mosquito movement behavior, host movement patterns, and host attractiveness to blood-seeking mosquitoes.

Analysis of the model produces new metrics of mosquito-borne pathogen transmission that show how host movement patterns, variation in host biting attractiveness, and landscape geometry combine to introduce heterogeneities into the transmission process. Although the consequences of heterogeneous transmission for disease dynamics have been investigated previously, mechanistic explanations of what underlies these heterogeneities have been lacking. Another poorly understood issue in spatial models throughout population ecology is the spatial scale at which encounters between individuals are well mixed. Using an evenness index applied to location- and individual-specific metrics of transmission, we show how mixing can be measured across scales.

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## Mathematical Modeling of Growth and Selenium Metabolism of *S. maltophilia* O2

*S. maltophilia* O2 was isolated from a mercury contaminated site in Oak Ridge, TN. This bacterium is able to survive and grow in the presence of several toxic metals including copper, mercury, lead, and selenium among others. Our study deals with selenite, an oxidized form of the element selenium. Normally, selenium is required in the diets of most organisms in trace amounts. However, an excess of selenium is toxic. *S. maltophilia* O2 is able to survive in the presence of toxic levels of selenite by reducing and precipitating it into non-toxic elemental selenium.

This study followed the growth of *S. maltophilia* O2 in the presence and absence of selenite by measuring turbidity and viable cell counts. Protein expression was studied via two-dimensional gel electrophoresis to identify any proteins which may confer selenite resistance. The selenium in the supernant and inside the cells was also measured. The growth of the control strain followed a classical growth curve with lag, log, and stationary phases. In the experimental group, the bacteria shifted from an exponential phase into a stationary phase after the addition of selenite.

Our mathematical model accounts for the bacterial growth and the selenite metabolism. It is based on a system of differential equations involving a modified logistic growth equation coupled with Michaels-Menten enzyme kinetics. The model predicts the bacterial biomass and the concentration of selenium in the supernant and inside the cells at any point in time. Analysis and comparison to experimental data was carried out using XPP and R. Parameters for the logistic growth model were determined by using the control group data and R's nonlinear least-squares regression software. The results of the mathematical model compared favorably with experimental data throughout the growth cycle and give a mechanistic model for the reduction of selenite by bacteria.

**Undergraduate Poster Session**

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## Modeling the mechanisms of naturally acquired immunity to malaria

Infection with *Plasmodium falciparum* can cause severe malaria in adults and children if they lack malaria-specific immunity. In residents of malaria endemic areas, naturally acquired immunity is first characterized by resistance to the clinical manifestations of malaria and eventually resistance to infection. Anti-malarial immunity may act at different stages of the parasite life cycle; liver-stage immunity would block the initiation of new infections and blood-stage immunity could block erythrocyte invasion and/or destroy infected RBC reducing Parasite Multiplication Rate i.e. the number on newly infected RBC (in which parasites survived until the next reinfection cycle) per one previously infected RBC.

In order to understand the impact of stage-specific immunity, we analyzed a treatment-time-to-reinfection study from Western Kenya, where 197 adults and children were treated with artemether/lumefantrin to clear blood-stage parasites. Individuals who had no detectable blood-stage parasites 2 weeks post-treatment were deemed cured and thus any parasitemia during the subsequent 10 week follow-up was considered a new infection. Children were further categorized into three age groups (0-4 yr, 5-9 yr and 10-14 yr). As previously observed, there was a progressive delay in mean time to reinfection associated with age and adults had lower parasite densities and fewer observed 'peaks' of parasites once infected compared to children.

To understand what forms of immunity could reproduce the observed reinfection curves for each age group we used a modeling approach. We first derived the reinfection functions assuming liver-stage (infection blocking) immunity only or blood-stage (growth slowing) immunity only and fitted them to experimental reinfection proportions. We found that the reinfection curves could be reproduced by the model with blood-stage immunity where each age group had a distribution in the parasite multiplication rate, with a decrease in the mean of this distribution with age.

To gain further insight into acquisition of immunity we developed a stochastic model of malaria infection and blood stage immunity, incorporating both a strain specific as well as a cross reactive or 'general' immunity to all strains. It was able to capture the observed reinfection rates, and remarkably also the observed levels of parasitemia. The model suggests the importance of rapidly-induced, strain-specific immunity in clearing individual infections, and slowly acquired general immunity in bringing down the average Parasite Multiplication Rate with age and magnitude of peaks of parasitemia.

Understanding the dynamics of naturally acquired immunity provides insights for malaria vaccine development as well as a tool for immuno-surveillance in areas experiencing changes in malaria epidemiology due to malaria control interventions.

When does overuse of antibiotics become a tragedy of the commons?

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Over-prescribing of antibiotics is considered to result in increased morbidity and mortality from drug-resistant organisms. A resulting common wisdom is that it would be better for society if physicians would restrain their prescription of antibiotics. In this view, self-interest and societal interest are at odds, making antibiotic use a classic ``tragedy of the commons''. Here we analyzed the decision to prescribe antibiotics as a mathematical game, and showed that this conflict of interest may indeed result, though not in all cases. Increased use of antibiotics by individuals benefits society under certain circumstances, despite the amplification of drug-resistant strains. In situations where increased use of antibiotics is worse for society, antibiotics may be harmful for the individual as well. For other scenarios, where a conflict between self-interest and society exists, restricting antibody use would benefit society. Thus, a case-by-case assessment of appropriate use of antibiotics may be warranted.

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## Dynamics of length distributions of in vitro intermediate filaments

Intermediate filaments are one of the cytoskeleton components. The cytoskeleton is an intracellular structure made of structural proteins polymerized in filaments that are organized into networks in the cytoplasm. Here a general method is given to study the temporal evolution of length distributions of filaments described as linear macromolecules. An aggregation model with explicit expression of association rate constants depending on the properties of interacting objects is considered. The rate constants are derived using Smoluchowski's theory. A set of hypotheses on the geometry and properties of interacting macromolecules is considered, leading to a collection of models. Fitting of model responses to experimental data yields the best-fit for each model in the collection. By using model selection, the more appropriate model to represent the assembly at a given time point is identified. Hence, conclusions on the object properties can be drawn.

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## Exclusion and spatial segregation in the apparent competition between two hosts sharing macroparasites

We investigate the spatial dynamics of a deterministic model describing two host species experiencing apparent competition mediated by macroparasites. The work is inspired to the system of rock partridge (*Alectoris graeca saxatilis*) and black grouse (*Tetrao tetrix*) sharing a common helminth parasite (*Ascaridia compar*) in a partially common spatial domain in the Italian Alps, and aims at elucidating the general mechanisms of apparent competition in a spatially structured environment.
First, we analyse the behaviour of a single-host macroparasite partial differential equation (PDE) model, both in the cases of uniform or spatially-dependent vital rates of the host, focussing on the role of spatial diffusion on parasite persistence and host abundance. We obtain the threshold condition for parasite persistence, and discuss how this depends on host diffusion coefficient; mpreover, we found (in contrast to what occurs in reaction-diffusion models for an isolated population) that, in the case of spatially-dependent vital rates, increasing the host diffusion coefficient generally results in an increase of the overall host population.
Afterwards, a PDE model featuring spatial diffusion and parasite-mediated competition between two species is analysed in order to understand the role of spatial heterogeneity in hosts coexistence. We assumed a partial overlap among the habitats of the two species, and we found that the shared parasites could cause, depending on the values of the diffusion coefficients of the species, a decrease of the realised habitat and, eventually, the extinction of the species less tolerant to parasite infection. This shows that the presence of regulating parasites renders rather complex the effect of dispersal on population dynamics, and that the dynamics of apparent competition cannot be adequately understood from spatially-independent models.

# EMERGENCE OF CELLULAR AGING FROM A GENE NETWORK MODEL

Hong Qin

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Why would a genotypically homozygous population of cells live to different ages? To address this question, I propose a mathematical model of cellular aging based on gene interaction network. This model network is made of only non-aging components, and interactions among genes are inherently stochastic. Death of a cell occurs in the model when an essential gene loses all of its interactions. The key characteristic of aging, the exponential increase of mortality rate over time, can arise from this model network with non-aging components. Hence, cellular aging is an emergent property of this model network. The model predicts that the rate of aging, defined by the Gompertz coefficient, is proportional to the average number of interactions per gene and that stochastic heterogeneity is an important factor in shaping the dynamics of the aging process. Preliminary experimental results to test the model predictions will then be presented.

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## Dendritic cell vaccines for cancer: a mathematical description.

An increasing number of medical researchers have begun to recognize the importance of harnessing a patient's immune system to combat cancer, and there is a wide array of immune therapies currently under investigation. One promising immune therapy is dendritic cell (DC) treatment. Dendritic cell treatment consists of injecting primed DCs into the patient to trigger an improved immune response to an existing tumor. There are several open questions in DC treatment. One is the timing of the doses: since the immune response is self-regulating, feedback mechanisms can reduce the effectiveness of the vaccine if the dose is too large or if the vaccine is given too often. Another open question is what impact the choice of injection site has on the efficacy of the therapy. In this mathematical model, we describe the trafficking and interactions of DCs and other immune cells in the body. Data from murine studies of the effect of DC injections are used to calibrate the model. The model allows us to investigate various cancer responses to treatment as DC injection sites and doses are varied.

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## Dynamics and evolution of complex food web networks

The importance of evolution to ecological dynamics is increasingly being recognized, as more evidence points to smaller differences in time scale than previously thought. Community dynamics and evolutionary processes appear to be especially important determinants of ecosystem response to environmental change. Recent studies of ecological networks have advanced our understanding of how evolutionary processes and ecological interactions such as omnivory, competition, and mutualism affect ecological structure and stability. These and other advances such as those in understanding the role of biodiversity in ecosystem function have motivated the development of community evolution models such as ours that helps understand ecological change and unify ecological theory by integrating community and ecosystem ecology with evolutionary biology.

Our model begins with relatively small food web networks (20 species or less) and evolves larger networks through a process of stochastic speciation and deterministic population dynamics. It is based on an allometric trophic network model that specifies food-web structure using a stochastic model of network architecture and community dynamics comprised of a set of ordinary differential equations that govern the change in species biomass over time. Speciation proceeds by introducing new species at low population densities with traits slightly different from randomly chosen parent species. Traits include body size, trophic generality, and diet based on location and feeding ranges within the one-dimensional community niche space. Network and species properties such as diversity and biomasses are subsequently tracked through time.

The resulting evolved ecosystem networks are highly diverse and exhibit realistic properties. They share many properties including network structure and body-size-abundance distributions with their empirical counterparts. Other networks are relatively short and fat (many species at few levels) or tall and thin (few species at many trophic levels). Including shared nutrient limitation among basal species increases the likelihood of obtaining more reasonable distributions of diversity among trophic levels. Connectance varies during community evolution. The generality, vulnerability and niche overlap of species and their neighbors within the network help determine which species persist and which go extinct. Whole-network properties of the food webs evolve in response to speciation as webs increase in complexity. This work shows how a few and relatively simple evolutionary and ecological assumptions and models can be integrated to help understand ecological change while yielding complex and realistic ecosystem structures through time.

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## A mathematical model of *Daphnia* epidemics: how resources and competitors alter the disease dynamics

*Daphnia dentifera* are small herbivorous crustaceans living in freshwater lakes and feeding on algae. They are being preyed upon by fish and other predators such as the phantom midge *Chaoborus* and they can become infected by the virulent fungus *Metschnikowia bicuspidata*. Once infected there is no recovery so *Daphnia dentifera* die releasing fungal spores. In many Midwestern lakes they can also compete for resources with *Daphnia pulicaria* which do not become infected by *Metschnikowia bicuspidata*.

Taking all the interactions into account we obtained a model with five populations: healthy *Daphnia dentifera*, infected *Daphnia dentifera*, fungal spores, algae, and *Daphnia pulicaria*. Specifically, we assumed that the *Daphnia* birth rates are nonlinearly dependent on the algae, background death and predation rates are constant and infectivity depends nonlinearly in the algae and the fungal spores. Infected hosts die at a higher rate due to the disease and because they are being preferentially preyed upon. The fungal spores released per infected hosts that die depend on the host growth rate.

The analysis of the model reveals multiple positive equilibria that undergo a wide variety of bifurcations. In the host – algae system we found an interior equilibrium that exhibits a supercritical Hopf bifurcation as the maximum feeding rate of the host increases. In the host – algae – inferior competitor system oscillations of the host and algae develop, while the competitor dies out. We also found a parameter domain of coexistence via a limit cycle. In the absence of the competitor, the system exhibits damped oscillations and disease is stabilizing. Finally, in the five-dimensional system friendly competition is observed which results in damped oscillations. Hence one might use the 'disease dilution' by inferior competitors as a strategy to control disease.

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## Reciprocal movements drive heterogeneity in pathogen transmission

Human movement strongly influences pathogen transmission. In directly transmitted diseases such as influenza, human movement has been shown to play a significant role at both a global scale and extremely fine scales (e.g. a single school). For sexually transmitted diseases, description of individual contact networks continues to be a popular method of identifying risk. Understanding where people go, how long they spend there, and what level of risk they are accruing during each visit is key to modeling and understanding the spread of pathogens in space and time as well as constructing optimal control strategies.

Unlike directly transmitted diseases, vector-borne diseases like malaria and dengue do not require two individuals to be at the same location in the same time period. In fact, given the intermediate vector step in the transmission cycle, sharing the same space at the same time as an infected individual confers no risk to susceptible individuals. However, an infective individual can expose multiple vectors. Once the pathogen has completed its incubation period within the vectors (assuming they survive long enough), identifying a single secondary infection could lead to finding other individuals who were also infected, provided one can identify who else was at the infested location at the point in the past when the infective vectors were active. Assuming people travel to the same places consistently through time, the movement patterns of an infective individual should contain the house they were infected in; one may expect to find other infective individuals in that single home. Though the movement patterns of an infective person can be a good indication of multiple locations where risk will be elevated in the future, one would not expect many of the houses an infective person visits to currently contain other infective individuals.

A recent study in Iquitos, Peru showed that not only are contact networks important indicators of risk for the vector-borne disease dengue, but also found patterns that indicate there may be further important structures of human movement. There were significantly more homes with at least one infective individual in the contact network of an infective individual than that of a non-infective individual. This difference strongly suggests reciprocal movement, where the contact networks of multiple individuals overlap.

In an attempt to show reciprocal movement can recreate the observed patterns, as well as get a crude understanding of the amount of overlap necessary, we created an agent-based model of dengue that explicitly defined movements of every individual. We varied the level of overlap and found that, in these simulations, only when there was a considerable level of overlap could we achieve results similar to those from the study. Future efforts will include using these models as a guide to inform the design of new studies to investigate the actual level of overlap in real cities, as well as understand the implications of various control efforts in light of extensive reciprocal movement. Preliminary work shows that when contact networks guide the locations of spraying, the presence or absence of reciprocal movement greatly changes the effect of the effort.

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## Investigating the role of tumor tissue architecture in chemotherapy: from tumor histopathology to drug efficacy

Part of the minisymposium “Data-driven modeling in Mathematical Oncology” organized by Dr. Banu Baydil

Abstract:
Poor penetration of the tumor tissue by drug particles contributes to low efficacy of therapeutic compounds, and, in many cases, results in the failure of the Phase II clinical trials, even if the therapeutic compounds were successful in laboratory experiments. This may be attributed, at least partially, to the fact that experimental models do not recreate the process of drug penetration into the tumor tissue in a way it takes place in the patient body. We developed a computational model of drug penetration that operates on the microscopic tissue scale and recreates various physico-chemical conditions of the tumors. This model integrates histopathology images of various tumor tissues, and includes explicitly defined tissue morphology that is comprised of individual and/or stromal cells surrounded by the interstitial space filled with the fluid that impacts drug transport. We investigated the dynamics of a class of drugs activated in regions characterized by either low oxygen or high acid levels, and showed that they may lead to shifting of the tissue metabolic profile. Our computational results showed that there is a non-linear relation between tissue permeability, its cellular density and penetration of drug molecules due to the convective interstitial transport. Moreover, we demonstrated that heterogeneity in tissue composition, such as irregular cell configurations, might solely be responsible for the emergence of tissue zones that are not exposed to drugs in concentrations sufficient to provide therapeutic action.

## The Endogenation of Immunization

**Timothy C. Reluga**
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Abstract:
Vaccines are one of our finest examples of scientific miracles -- they are cheap, easily administered, and provide life-long protection against dangerous and deadly infectious diseases. However, the long-term sustainability of the current vaccine economics is uncertain. The interaction of economic and biological factors means some important vaccines are not universally available today. And the reliance of vaccines on centralized production introduces hysteresis leaving production can be sensitive to sudden transitions in national economic structure. In this talk, I'll explore some new mathematical models that couple macroeconomic dynamics with epidemiological dynamics, investigating the existence of alternative "solutions" with endogenous immunization systems and possible transition paths to these new systems.

**Alan Rendall**, Max Planck Institute for Gravitational Physics, Potsdam, Germany

## Mathematics of the NFAT signalling pathway

NFAT (nuclear factor of activated T cells) is a transcription factor which plays an important role in various signalling pathways. One of these contributes to transmitting the information that an antigen has been encountered from the T cell receptor to the nucleus. This causes the transcription of the interleukin 2 (IL-2) gene, a key early event in T cell activation. In more detail, the recognition of an antigen by the T cell receptor, combined with a suitable costimulatory signal, leads to a flux of $Ca^{2+}$ into the cytosol and the dephosphorylation of NFAT by calcineurin. The NFAT then moves into the nucleus and can take part in transcription.

The process just described has been modelled mathematically by Salazar and Höfer [1]. In the resting cell NFAT is phosphorylated at thirteen sites and the sequential dephosphorylation at these sites leads to a digital effect in an individual cell. Thus after activation almost every cell either produces IL-2 at a maximal rate or produces almost none. The model uses a system of 56 ordinary differential equations with 134 parameters, where the unknowns are the concentrations of different phosphorylation states of NFAT in the cytosol and in the nucleus. The analysis of [1] is based on an examination of a certain steady state of this system for each choice of the parameters. In [2] a more global understanding of the system was obtained. It was shown that the steady state of the system considered in [1] is the only one for a given choice of the parameters and that all other solutions converge to the steady state.

These results were proved using the Deficiency Zero Theorem of Chemical Reaction Network Theory (CRNT). Apart from the interest in understanding this particular system this is an example of the power of CRNT for obtaining rigorous mathematical results about large systems of ordinary differential equations containing many parameters of the kind which often come up in modelling biological systems. In [2] it was also examined what happens when the constant concentration of calcineurin in the model of [1] is replaced by the time-dependent concentration coming from a dynamical model of the calcium influx. Parameters were identified for which the calcineurin concentration tends to a constant and the analysis of the more complicated model can be reduced to that of the previous case.

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## The Dynamics of Wound Healing With Elevated Cortisol Levels.

During the wounding healing process many complex interactions occur between fibroblasts immune cells and immune mediators. These interactions determine whether or not the wound will heal or become chronic. Cortisol is a stress hormone that remains elevated when individual are stressed. It acts as an anti-inflammatory mediator and delays wound healing.

To better understand the wound healing in trauma patients, we have developed a system of differential equations modeling the dynamics between local fibroblast, neutrophils, macrophages, collagen and the systemic mediator Cortisol. This model is calibrated using data from wounded, restrained (stressed) animals. Using this model, we focused on the accumulation of collagen in an oxygen-deprived wound (diabetes) with and without trauma (high cortisol levels).

**Racheal L Cooper**, Virginia Commonwealth University, Richmond, VA, USA

## A Subsystem Approach to Understanding the Inflammatory Response in a Wound.

The inflammatory response in a wound is composed primarily of neutrophil and macrophage cell activity. This work uses an ODE subsystem approach to investigate the relative dynamics of these two cell populations in response to debris, including platelets and pathogens. Experimental data from Broughton et al. (2006) and Leibovich & Ross (1975) were used as validation and steady state analysis was performed. This model will be included in a larger wound healing model to explore the effect of cortisol on wound healing.

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## The Role of Metabolic Heterogeneity and Microenvironmental Selection in Tumor Growth and Treatment

Heterogeneity of the tumor and its microenvironment is now widely accepted fact in cancer biology. Here we specifically focus on heterogeneity of the metabolic cellular phenotype and within the environmental factors that influence it. Using a hybrid multi-scale mathematical model of tumor growth in a vascularized tissue, we investigate the selection pressures exerted by the tumor microenvironment as the cancer progresses. A key feature of the model is the focus on both normal and tumor metabolism. The metabolic phenotype of tumor cells is allowed to drift, and selection due to the microenvironment leads to increased glycolysis and decreased pH. Once this aggressive phenotype emerges, the tumor dramatically changes its behavior due to acid-mediated invasion, an effect that depends on both phenotypic and spatial arrangement of the tumor. In early stages of growth, the tumor is stratified, with the most aggressive cells developing and residing within the interior of the tumor. Eventually, these aggressive cells can grow out to the edge of the tumor and invade into the normal tissue by causing acidosis. The model is supported by experimental results from both murine and clinical data.

Results from the model suggest that diffusible cytotoxic treatments such as chemotherapy may increase the metabolic aggressiveness of a tumor post-treatment due to the altered selection pressure caused by the drug. Chemotherapy removes the metabolic stratification of the tumor and allows more aggressive cells to grow towards blood vessels and normal tissue. In contrast, a second type of therapy that buffers the extracellular pH significantly slows down the development of aggressive tumors if the treatment is given early enough. However, if the tumor reaches critical mass and begins to invade, the buffering treatment has little effect, suggesting that this approach is preventative but not curative. A third treatment we consider is the use of anti-angiogenic therapy, which foments the development of aggressive phenotypes due to degradation of the tumor microenvironment.

All of these simulated treatments highlight the importance of the dialogue between tumor and environment and critically how this dialogue modulates heterogeneity driving the tumor down very different evolutionary paths.

**Michael A. Robert**, Kenichi Okamoto, Alun L. Lloyd, and Fred Gould
North Carolina State University, Raleigh, NC, USA

## A Mathematical Model for Assessing the Reduce and Replace Strategy for Combating Dengue Transmission by *Aedes aegypti*

Traditional methods of controlling the primary vector of dengue fever, *Aedes aegypti*, have not been sufficient for controlling the disease itself. Despite an increase in surveillance as well as increased implementation of vector control strategies, dengue remains endemic in many parts of the world. In the last decade alone, a number of novel strategies, including those involving genetically modified mosquitoes (GMM), for controlling *Ae. aegypti* have been proposed and investigated. Strategies involving GMM typically have one of two general goals: Population replacement or population reduction. In the former, GMM would be released that carry an anti-pathogen gene so that mosquitoes that inherit the gene would not be able to transmit disease. In the latter, GMM would be released that pass on lethal genes to their offspring so that after many generations and continued releases, populations near extinction.

In this presentation, we propose and evaluate the potential of another novel strategy which combines the two general goals of GMM strategies. This strategy, henceforth known as Reduce and Replace (R&R), aims to introduce mosquitoes with a single genetic construct that causes female-specific lethality while simultaneously introducing anti-pathogen genes into that population. Using numerical simulations of an ordinary differential equation model, we explore the efficacy of the R&R strategy. We compare several strategies that involve the release of R&R mosquitoes in concert with GMM that confer lethal genes or those that carry only anti-pathogen genes.

We find that the continued release of R&R mosquitoes alone can successfully replace a wild population with one that cannot transmit dengue fever if there are no fitness costs associated with the transgenes involved. If there is a fitness cost associated with carrying the transgenes, continued release of R&R or anti-pathogen only mosquitoes would be required to maintain a low frequency of competent vectors. We find that introducing mosquitoes with lethal genes only before introducing R&R mosquitoes does not, in general, lead to a lower frequency of competent vectors than other strategies. Our model suggest that a release of R&R mosquitoes followed by a release of mosquitoes carrying only an anti-pathogen gene lowers the number of competent vectors more than any other single or combined strategy we consider; however, the R&R strategy on its own underperforms when compared to a combined strategy of R&R and anti-pathogen only mosquitoes.

We discuss the R&R strategy as a component of integrated pest control and motivate the need for further assessment of the utility of this strategy before testing of its efficacy begins.

**Ignacio Rodriguez-Brenes**, Department of Mathematics, University of California, Irvine, CA, USA

## Evolutionary Dynamics of Feedback Escape and the Development of Stem-Cell-Driven Cancers

Cancers are thought to arise in tissue stem cells, and similar to healthy tissue, are thought to be maintained by a small population of tumor stem or initiating cells, whereas the majority of tumor cells are more differentiated with limited replicative potential. Healthy tissue homeostasis is achieved by feedback loops, and particular importance has been attached to signals secreted from differentiated cells that inhibit stem-cell division and stem-cell self-renewal, as documented in the olfactory epithelium and other tissues. Therefore, a key event in carcinogenesis must be escape from these feedback loops. In this talk we present an evolutionary computational model of feedback escape in cancer. We find that out of all potential evolutionary pathways, only one unique sequence of phenotypic transitions can lead to complete escape in stem-cell-driven tumors, even though the required mutations for these transitions are certainly tissue specific. This insight, supported by data, facilitates the search for driver mutations and for therapeutic targets. Different growth patterns can result from feedback escape, which we call “inhibited”, “uninhibited”, and “sigmoidal”, and which are found in published data. The finding of inhibited growth patterns in data indicates that besides architecture, the regulatory mechanisms of healthy tissue continue to operate to a degree in tumors.

**Lisa Rogers**, Courant Institute of Mathematical Sciences, NY, NY, USA
Charlie Peskin, Courant Institute of Mathematical Sciences, NY, NY, USA

**Keywords** Computational Biology, Neurobiology, Regulatory Networks, Systems Biology

**A Mathematical Model of the Sleep/Wake Regulatory System**

The mammalian sleep/wake system is governed by several interacting populations of neurons in and around the hypothalamus. We present here a model of the sleep and wake promoting neuron populations in the ventrolateral preoptic nucleus (VLPO), basal forebrain (BF), parabrachial nucleus/precoeruleus area (PB/PC) and laterodorsal tegmental/pedunculopontine tegmental nucleus (LDT/PPT). The model is formed using Morris-Lecar firing dynamics for electrical input and chemical kinetics of receptor-neurotransmitter/neuromodulator interaction to quantify chemical synaptic input. We also present a novel but simple way of relating firing rates of neuron populations to corresponding concentrations of neurotransmitter/neuromodulator, allowing us to track both electrical and chemical output. Rate and equilibrium constants are obtained using appropriate mammalian data from the BRENDA enzyme database.

**Nick A. Rohacz**, Loyola Marymount University, Los Angeles, CA, USA
Katrina Sherbina, Loyola Marymount University, Los Angeles, CA, USA
Kam D. Dahlquist, Loyola Marymount University, Los Angeles, CA, USA
Ben G. Fitzpatrick, Loyola Marymount University, Los Angeles, CA, USA

## Continuous Time Markov Chain Models of Gene Regulatory Networks under the Environmental Stress of Cold Shock in *Saccharomyces cerevisiae*

In this poster, we present our recent efforts in building and analyzing a stochastic model of gene regulatory networks. The approach we have taken uses techniques of continuous time Markov chains or jump-Markov processes to model complex interactions of regulatory dynamics. This coupled with a stochastic approximation technique allowed for comparing the model to data.

Data in this poster comes from DNA microarrays measuring gene expression in budding yeast (*Saccharomyces cerevisiae*) as it responds to a cold shock environmental stress. The wild type strain BY4741 and strains deleted for the genes that encode the Cin5, Gln3, Hmo1, and Zap1 transcription factors were harvested during early log phase at 30ºC (the control condition). Cells were subsequently harvested at 15, 30, and 60 minutes after being subjected to 13ºC cold shock (the stress condition). Four to five replicates were performed for each strain and time point. Total RNA was purified from each sample, labeled and hybridized to DNA microarrays. Each cold shock time point (labeled with Cy5) was competitively hybridized with labeled aRNA from the $t_0$ control time point (labeled with Cy3). The orientation of the Cy3 and Cy5 dyes was swapped for two of the replicates for each strain. Within-chip normalization was conducted using the limma package in the R Statistical computing environment and chip-to-chip normalization was conducted using an in-house developed median absolute deviation scaling. These data provide gene expression levels of the cold shocked yeast relative to their expression at 30ºC.

Changes in gene expression due to cold shock are controlled by a network of transcription factors which bind to regulatory DNA sequences. A gene regulatory network for the cold shock response was constructed from a set of transcription factors that are known to regulate each other as documented in the YEASTRACT database. Transcription factors were included in the network if their target genes were enriched in a list of genes that had significant differential expression in the microarray data or if there was other experimental evidence suggesting their involvement in the cold shock response. The resulting network consists of 21 nodes, each of which represent the gene, the mRNA, and the protein transcription factor it encodes, assuming that a gene is translated into protein as soon as it is transcribed. These nodes are connected by 50 directed edges which represent the regulatory relationships, either activation or repression.

The state of each gene in the network is modeled in a discrete manner as being up-regulated, down-regulated, or unchanged under the stress condition, relative to the control condition. The states of the genes controlling each target gene, along with weighting parameters, determine the likelihood of the target making a transition from one state to another. As a complex, high-dimensional stochastic dynamical system, the model must be simulated with Monte Carlo techniques to observe and understand the output. More importantly, stochastic optimization techniques are required to compare simulations to data in order to estimate the model parameters. We will present in this poster our progress in simulation and estimation of network parameters governing *S. cerevisiae*'s response to cold shock.

This work was supported by NSF award 0921038 (KDD, BGF, KS) and the McLaughlin Chair of Biology (KDD, NAR).

**Robert J Rovetti**, Loyola Marymount University, Los Angeles, CA, USA

## Characterizing the behavior of a probabilistic lattice model of cardiac calcium release under different spatial and geometric conditions

We present a simulation study of a probabilistic discrete-time two-state lattice model that replicates physiological features of calcium release units within a cardiac cell, including threshold excitation, refractory period, and spatial interactions. Of particular interest is the emergence and persistence of periodic-like behavior in the ensemble average state value over time. After varying system size, aspect ratio, and maximum distance for spatial coupling, we find that stable (nonperiodic) behavior from beat to beat is best reinforced by a slightly oblong shape, a minimum size, and a restriction of spatial interactions to nearest-neighbor coupling, all of which are characteristic of mammalian cardiac cells. We also explore the consequences of imposing distributions on the underlying parameters of the model, mimicking the variability of number of channels and geometric arrangement of the release units in the cell.

**Carly Rozins**, Queen's University, Kingston, ON, Canada

## Forest Stability Analysis Through Percolation Theory and Mycorrhizal Networks

Mycorrhizal fungal networks occur where mycorrhizal fungal mycelia link the roots of multiple plants creating a connected network. Mycorrhizal fungi are then able to promote the interplant transfer of minerals, carbon and water. The mycorrhizal fungus mycelia have been shown to shuttle carbon, nutrients and water from mature trees and nutrient dense areas to nutrient limited trees such as to seedlings. Mycorrhizal networks allow seedlings to mature underneath the tree canopy. A feat unattainable without the aid of the fungal partners. Here we analyze the stability of forest communities, by examining the forest connectedness and ability to rebound after disturbances as facilitated by mycorrhizal networks. Within a forest community, a Hub tree is a tree who's roots are highly connected to many neighboring tree roots by mycorrhizal fungal mycelia. Hub trees for mycorrhizal networks have been shown to even out resource availability and create favourable local conditions for tree establishment. These Hub trees are thought to be fundamental in forest community restoration and development.

It has been shown that the stability of forest ecosystems is in the existence of biological networks. By forming a mycorrhizal network, the community becomes more stability and regenerates following a disturbance more quickly. In particular, it has been thought that if hub trees remain after a disturbance, along with their fungal symbiotic partners, then forest regeneration is achieved more quickly. Here we mathematically explore these ideas with the aid of graph and percolation theory.

A random graph is a collection of nodes (or verticies) linked together at random by lines (or edges). Graph theory has been used to study a wide variety of real-world networks such as the Internet, social networks, power grids as well as epidemiological networks. We show that graphs and percolation theory may be useful tools at modelling the flow of nutrients and carbon between trees in a mycorrhizal network. And hence a useful tool for an analysis of forest stability. For this particular model, trees represent the nodes of the graph and the mycorrhizal fungal mycelia, which links the trees together, are represented by the edges of the graph. Through percolation theory, it has been suggested that if connection patters are chosen appropriately, a network can be made highly resilient to random deletion of nodes. Alternatively they might be susceptible to attacks, which specifically target nodes of high degree (ie. Hub trees).

The connectivity of the forest community and hence the robustness of the graph is analyzed after random depletion of edges and nodes. By assuming a relatedness between tree connectedness and maturity (and thus ability to produce carbon and acquire nutrients), we are able to quantify the robustness (ie. the ability to regenerate after a disturbance) of forest communities. As in other studies, by deriving the probability generating functions specific to the mycorrhizal network, we are able to calculate the average large component following a random deletion, as well as targeted deletion of nodes and edges. This provides us with an analysis of forest stability and the importance of key hub trees within communities. Such findings may be useful in adjacent disciplines such as forestry where quick forest regrowth is economically and ecologically favourable.

**Dan Ryan**, NIMBioS, University of Tennessee, Knoxville, TN, USA

## A Cross-diffusion Model for Avoidance Behavior in an Intraguild Predation Community

Intraguild predation (IGP) refers to a community module that blends competitive and predator-prey dynamics. Although IGP is widespread in nature, spatially homogeneous models for IGP communities predict that stable coexistence is only possible if restrictive conditions on resource productivity, competitive ability and predation susceptibility are satisfied. This talk will consider the population dynamics of an IGP module in a spatially heterogeneous landscape and examine how avoidance strategies deployed by the intraguild prey can lead to more robust coexistence states.

**René A. Salinas**, Appalachian State University, Boone, NC, USA

## Using an Individual-Based Model to Study the Spread and Control of Pseudo-rabies virus in Feral Hogs in Great Smoky Mountains National Park

For over two decades, the Park Service has been removing feral hogs from Great Smoky Mountains National Park (GSMNP) in a attempt to control the population. In 2005, the first seropositive cases of pseudo-rabies virus (PRV) were recorded in harvested individuals. We developed an individual-based model (IBM) for the feral hog population in Great Smoky Mountains National Park (GSMNP) and surrounding regions to test theories on the spread of pseudo-rabies virus (PRV) in GSMNP. Because there is limited understanding of the spread of the disease in feral populations, an IBM is well suited to test both modes and effectiveness of transmission. Another advantage of the IBM approach is the ability to model the efficiency of control methods (harvesting) for mitigating disease spread. IBMs can be used to compare changes in location, time, and effort to determine optimal control strategies. In this presentation I will describe the disease components of the model and present preliminary results on the effectiveness of the current harvesting strategy on the population density of hogs and the spread of PRV. Results suggest that although the year-to-year variation in fall hard mast is a natural population regulator, harvesting has had a impact on the population. This work is part of a NIMBioS Working Group that includes: Bill Stiver, Joseph Corn, Suzanne Lenhart, Chuck Collins, Marguerite Madden, Eric Carr, Brandon Schmidt, Ellen Kasari, Kurt VerCauteren, Agricola Odoi, Hamish McCallum, and Graham Hickling.

**Ori Sargsyan**
Theoretical Biology and Biophysics and Center for Nonlinear Studies, Los Alamos National Laboratory, Los Alamos, NM, 87545, USA

## Analytical framework for identifying and differentiating recent hitchhiking and severe bottleneck effects from multi-locus DNA sequence data

Hitchhiking and severe bottleneck effects have impact on the dynamics of genetic diversity of a population by inducing homogenization at a single locus and at genome-wide scale, respectively. As a result, identification and differentiation of the signatures of such events from DNA sequence data at a single locus is challenging.

In this talk I will present an analytical framework for identifying and differentiating recent homogenization events at multiple neutral loci in low recombination regions. The dynamics of genetic diversity at a locus after a recent homogenization event is modeled according to the infinite-sites mutation model and the Wright-Fisher model of reproduction with constant population size. In this setting, I derived analytical expressions for the distribution, mean, and variance of the number of polymorphic sites in a random sample of DNA sequences from a locus affected by a recent homogenization event. Based on this framework, three likelihood-ratio based tests are developed for identifying and differentiating recent homogenization events at multiple loci.

Lastly, I apply the framework to two data sets. First, I consider human DNA sequences from four non-coding loci on different chromosomes for inferring evolutionary history of modern human populations. The results suggest, in particular, that recent homogenization events at the loci are identifiable when the effective human population size is 50000 or greater in contrast to 10000, and the estimates of the recent homogenization events are agree with the “Out of Africa” hypothesis. Second, I use HIV DNA sequences from HIV-1-infected patients to infer the times of HIV seroconversions. The estimates are contrasted with other estimates derived as the mid-time point between the last HIV-negative and first HIV-positive screening tests. The results show that significant discrepancies can exist between the estimates.

## Where to draw one's theoretical boundary: One system, one data set, two published models, two opposing conclusions

**Natasha Savage**
Duke University, Durham, NC, USA

Where to draw the theoretical boundary when modeling complex systems is an important problem. The modeler would like to capture all aspects of the system necessary for describing the phenomena of interest. The general goal is to create the simplest model that retains all relevant information, thus reducing parameter space, maybe allowing for analytical solutions, but generally making it easier for the modeler to gain insight about the real system. The talk will discuss the published work of two groups within the field of yeast cell polarity[1][2]. Both groups present a model describing the establishment and maintenance of the 'polarity patch', an isolated patch of protein on the cell membrane marking the presumptive bud site. While both models are designed to represent the same system and set their parameters using the same data, they differ in their level of abstraction and draw opposing conclusions. The comparison between these two models provides an interesting illustration of the importance of setting the theoretical boundary.

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**Steffen Schaper**, University of Oxford, Oxford, UK
Ard A. Louis, University of Oxford, Oxford, UK

## Predicting and preventing evolution from the knowledge of neutral spaces

In recent years, our understanding of molecular processes in medicine has exploded. One of the promises of this advance is the ability to tailor compounds for the treatment of specific pathogens. On the other hand, many drugs eventually stop being effective when pathogens evolve resistance. In this talk, we give a description of the evolutionary race to resistance, focusing on the importance of molecular details through the genotype-phenotype (GP) map. This map determines how the outcome of mutations at the genotype level induces phenotypic variation and thus triggers natural selection.

Often, single mutations do not change the phenotype but instead connect genotypes with the same phenotype to form a neutral space. These neutral spaces can be vast even for very small molecular systems; reasonably large molecules will most likely have neutral spaces that are much bigger than most reasonable populations. The discovery of an advantageous phenotype (the 'target') is then a search problem in a vast space (the 'source'). We characterize this search in terms of the frequency of the target in the mutational neighborhood of the source space. We study a simple model ignoring correlations between genotypes and find that the difficulty of the search problem is simply related to the inverse of this frequency.

Under low mutation rates, genetic drift leads to a localization of the population in genotype space. Thus exploration is limited to the immediate neighborhood of the population, and transitions between neighborhoods only occur when a neutral mutant goes to fixation. Between two fixations, large enough populations will thus repeatedly produce the currently accessible phenotypes. Intuitively such bursts increase the probability of that an advantageous mutant is fixed once it is discovered. Consequently, we probably cannot prevent the evolution of drug resistance when adaptive phenotypes are readily available. Instead we should aim to prevent the discovery of the target.

The effect of bursts is even stronger in realistic GP maps, which show strong correlations between similar genotypes. As an example, we study the folding of RNA sequences into secondary structures where the biophysical details are relatively well understood. We show how Watson-Crick base-pairing causes the fragmentation of neutral spaces into disjoint components. Furthermore, we find that the components can have intricate internal structure, and that connections to alternative phenotypes are not homogeneously distributed. While averages of the evolutionary process are still described reasonably well by our theory, fluctuations become more important in the presence of genotype correlations. In particular, both the size and temporal separation between bursts can increase.

All these findings underline the central role of the GP map for evolutionary dynamics. They also suggest how the course of evolution may be influenced. We discuss one possible approach to prevent, or at least delay, the evolution of resistance to drugs. When adaptive mutants are not immediately accessible, we can delay their discovery by a drug that removes genotypes on the path to discovery from the neutral space. This result suggests that drugs should be designed not only to be effective against the pathogens in their current state, but that evolutionary pathways can and should be taken into account.

**Tina Anne Schuetz**, Institute of Medical Engineering, Graduate School for Computing in Medicine and Life Sciences, University of Luebeck, Luebeck, Germany
Stefan Becker, Institute of Medical Engineering, University of Luebeck, Luebeck, Germany
Andreas Mang, Institute of Medical Engineering, University of Luebeck, Luebeck, Germany
Alina Toma, Institute of Medical Engineering, University of Luebeck, Luebeck, Germany
Thorsten M. Buzug, Institute of Medical Engineering, University of Luebeck, Luebeck, Germany

## A mathematical multiscale model of the role of microRNA-451 in glioblastoma growth

Glioblastoma (GB) is the most aggressive primary brain tumor and even with the most recent therapies median survival is only about 12 months.To aid the better understanding of tumor growth as well as the development and improvement of therapies computational modeling can be employed. In this work we introduce a multiscale model covering the molecular and microscopic scale. The model combines a molecular interaction network representing the influence of glucose and microRNA-451 (miR-451) on the subcellular level with an agent based model (ABM) for the cellular scale.

Many cancer cells utilize glucose to pursue proliferation and under unfavorable glucose conditions they migrate to more beneficial sites to avoid metabolic stress. In [2] it was shown that the level of miR-451 in GB cells is elevated under normal glucose conditions and decreased in a low glucose environment. MicroRNAs are short (22 nucleotides long) non-coding RNAs that regulate the expression of approximately 60% of all human genes at the post-transcriptional level. As one of these genes MO25 is targeted by miR-451. The MO25 protein binds to the protein LKB1 and this complex activates the AMPK and MARK3 signaling pathways, by that either initiating cell migration (low glucose environment) or cell proliferation (high glucose environment).

We translated the above described biological processes that take place within each GB cell into a molecular interaction network that is represented by ordinary differential equations (ODEs). In total 17 molecular species are involved whose concentrations constitute the 17 variables of the system which are governed by 17 ODEs. We then reduced the system to a total number of 12 variables and 12 ODEs by eliminating the five variables and equations that are merely part of a complementary pair, i.e. describing the phosphorylated and non-phosphorylated form of a protein or the active and inactive form of a protein. By following the approach introduced in [1] we coupled this subcellular interaction network with an ABM to also investigate the tumor development on a microscopic scale. The tumor cells represent the agents that are placed on a regular square grid. Initially, a constant glucose concentration is assumed on the whole grid. Over time, glucose is consumed by the cells influencing the molecular interaction network and diffuses through the grid as mathematically described by a partial differential equation. In each time step for each cell first the molecular interaction network will be evaluated. Then, based on the concentrations of phosphorylated MARK3 and active mTORC1 the cell's phenotype is determined as either proliferating, migrating or quiescent. Finally, cell migration and the spatial placement of daughter cells follows the gradient of a chemotactic agent (glucose).

First results show that the above described model is capable of reproducing the results obtained from biological experiments. We simulated the development of the in silico tumor under different glucose conditions chosen to be in accordance to the migration array experiments in [2]. The results demonstrate that under low glucose conditions a tumor tends to migrate faster and further than under medium glucose conditions. This is qualitatively in good agreement with the results of the in vitro experiments in [2]. In particular under low glucose conditions, the simulated tumor exhibits a behavior that is essential for the aggressive character of GB tumors: individual cells separate from the tumor bulk and invade the surrounding (healthy) microenvironment.

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## Using a Mathematical Model to Analyze the Treatment of a Wound Infection with Oxygen Therapy

**Richard Schugart**
Western Kentucky University, Bowling Green, KY

A mathematical model was developed to treat a wound with a bacterial infection using oxygen therapy. The model describes the relationship among neutrophils, bacteria, oxygen, cytokines, and reactive oxygen species. A quasi-steady-state assumption was introduced to reduce the model down systems of two and three equations. A mathematical analysis on the reduced model and simulation results will be presented in this talk.

## Understanding viral escape from the cellular immune response using computational modeling.

**Elissa Schwartz**
Department of Mathematics, School of Biological Sciences, Washington State University

Understanding viral escape from the cellular immune response using computational modeling Currently, efforts are underway to develop vaccines for several viral infections, including Human Immunodeficiency Virus type 1 (HIV-1). Development of a vaccine for HIV-1 is a challenge in part because rapid replication and mutation allow the virus to escape from the immune response. In this talk, I will present a computational model that simulates the cellular immune response to viral infection, including viral mutation and escape. The model reproduces the phenomena seen in clinical data from HIV-infected individuals. The results of the model can be used to predict virus and immune system interactions and to suggest conditions under which a vaccine would be most effective. These studies are useful to guide future strategies for the development of vaccines and other preventative or therapeutic interventions.

# Nature vs nurture in cancer initiation in hierarchical cell populations: a computational model.

**Jacob G Scott**[1,2†] and David Basanta[1]
1. Integrative Mathematical Oncology, H. Lee Moffitt Cancer Center and Research Institute
2. Centre for Mathematical Biology, Oxford University

The cancer stem cell hypothesis states that tumors are sustained by an immortal, stem-like (pluripotent) side population of cells that are capable of recapitulating the entire tumor bulk and associated heterogeneity. The existence of cells with these properties have been shown in a wide variety of fluid and solid malignancies and there has been significant work done to elucidate the importance of these cells from a therapeutic and biological standpoint without much success. While there is no doubt that cells with this sort of capacity can be found in tumors, further understanding of this hypothesis through experimental means remains extremely difficult - leaving the onus largely on theoreticians at this time.

To this end, we have built a hybrid cellular automaton model of a stem hierarchical tissue designed to represent a glioblastoma, the most common primary tumor of the brain with no known cure. This model represents the cells as discrete agents with specific, rule based activity and interactions and represents the milieu in which the agents live by a continuously defined space defined by oxygen. Cells of three types - glioma stem cells (GSCs), transient amplifying cells (TACs) and terminally differentiated cells (TDs) - make up the cellular population, and the microenvironment is described fully by a vascular architecture of varying density and oxygen which diffuses in a Fickian manner from these vessels and is consumed by the cells.

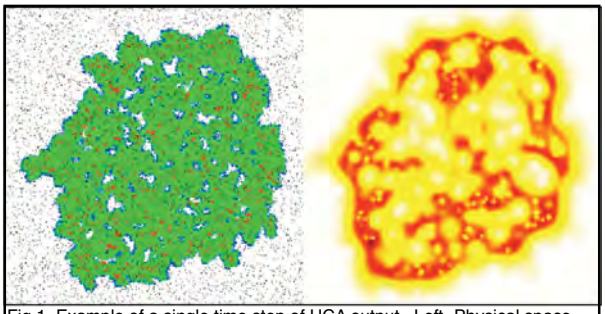


Fig 1. Example of a single time step of HCA output. Left -Physical space representation with GSC (red), TAC (green) and TD (blue) and vessels (black). Right - Microenvironment representation with oxygen tension represented by a heat map.

We present results germane to tumor initiation and progression with specific attention paid to stem cell phenotypes that promote these events. Specifically, we have found that there is a small band in the TAC phenotype governing rounds of division that promotes tissue overgrowth (tumorigenesis) that is conserved across other values for symmetric division and vascular density, suggesting the critical role that these TACs play (Fig 2.). Further, we have found that the microenvironment, in this case defined by vascular architecture, seems to play little role in cancer initiation and progression in the tissue size ranges considered ($<10^6$ cells) and that the stem cell phenotype governing symmetric/asymmetric division is only important when the TACs can divide less than 12 times.

We will also present pilot biological experiments designed and carried out to parameterize this model as well as several novel hypotheses concerning tumor vasculature and the role of stem cells in its creation.

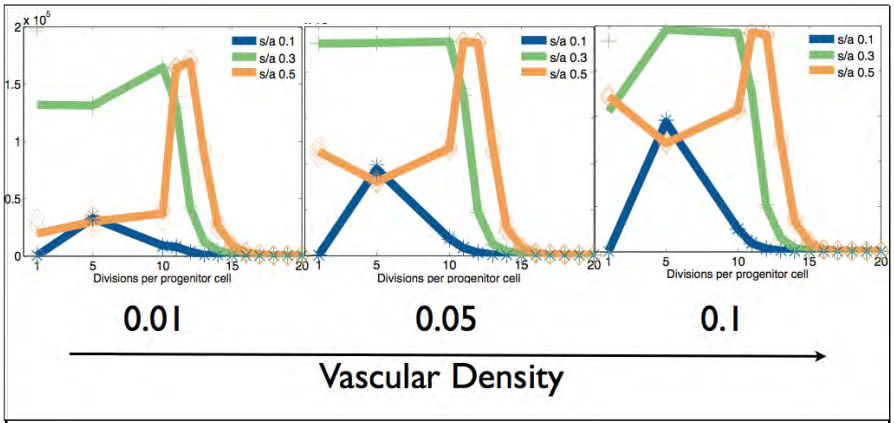



Fig 2. Exploring the parameter space with many iterations of the stochastic model we find that the model is extremely sensitive to perturbations in the number of divisions allowed for TACs with a 'sweet spot' between 12 and 14, above which the tissue never overgrows and below which it is sensitive to vascular density.

**Rebecca Segal**, Virginia Commonwealth University, Richmond, VA, USA

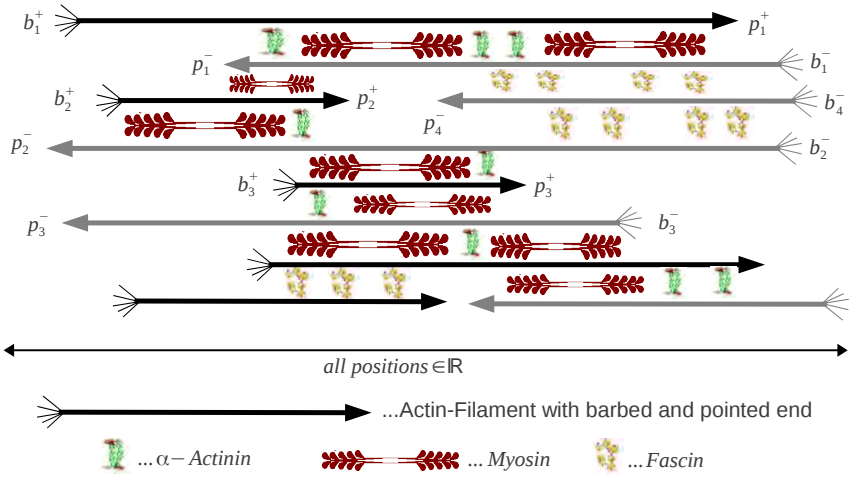
## Overview of Modeling Techniques for Wound Healing

Recent advances in wound healing have occurred from many directions. ODE models are used to track variations in cell and chemical concentrations during the course of wound healing, to explore parameter sensitivity and to identify possible treatment therapies. PDE models are used to track blood vessel formation, investigate tissue matrix repair and to understand the spatial dynamics involved in the healing process. Agent based and stochastic models are used to investigate patient specific variables and to understand patient variability in wound healing outcomes. This talk will present an overview of the recent developments in the field and begin the conversation about how the different results can be combined into a comprehensive model.

**Dietmar Oelz**, Mathematical Biology Group, Johann Radon Institute for Computational and Applied Mathematics (RICAM), Vienna, AUSTRIA

## Modelling contractility and antiparallel flows in actomyosin bundles.

I present a mathematical model in 1-D for an actomyosin bundle featuring antiparallel flows of antiparallel F-Actin. The model is able to relate these flows to the effect of cross-linking and bundling proteins and to the forces due to myosin II filaments and to stretching forces at the extreme tips of the bundle.
The modelling is based on a coarse graining approach starting with a microscopic model which includes the description of chemical bonds as elastic springs and the force contribution of myosin filaments.




In a second step we consider the asymptotic regime where the filament lengths are small compared to the overall bundle length and restrict to the highest order contributions. There, it becomes appearent that bundling proteins provide the viscosity of the filemant gel and are reasponsible for force transmission. Myosin filaments generate forces which are partly compensated by drag forces due to cross-linking proteins.
The model is able to explain how the bundle of comparatively short Actin filaments interspersed with myosin II filaments can effectively contract the two tips of the actomyosin bundle. It gives a quantitative description of these forces and of the antiparallel flows of the two phases of antiparallel F-Actin.

**Muhammad Shamim**, Rice University, Houston, TX, USA
Dr. Jennifer Young, Department of Computational and Applied Mathematics, Rice University, Houston, TX, USA

## A Comprehensive Framework for Modeling Intestinal Smooth Muscle Cell Contraction with Applications to Intestinal Edema

The contraction of intestinal smooth muscle cells (ISMCs) is a complex process, involving many chemical reactions and mechanical triggers working to produce the contraction-relaxation cycle. Due to its complexity, it is difficult to isolate the effect of one factor on the overall process. Mathematical modeling allows one to test various combinations of parameters and structural geometries to assess their effects on the process. Here we present a comprehensive mathematical model of the contraction of an ISMC from its initial innervation by the neurotransmitter acetylcholine to the final mechanical contraction. To the best of the authors′ knowledge, this is the first framework of its kind to model the phenomenon from innervation to mechanical contraction, incorporating both chemical and physical models.

A motivating factor for developing such a model is to understand the effects of intestinal edema on ISMC contractility. Intestinal edema refers to the excess accumulation of fluid in the interstitial spaces between tissue cells of the intestinal wall. Intestinal edema often leads to ileus, a decrease in intestinal transit due to a decrease in ISMC contractility. The link between edema and ileus is unknown and is the subject of current experimental research. One hypothesis is that the increase in fluid volume creates larger neuromuscular junction distances over which neurotransmitters must diffuse, diluting their transmission, consequently leading to reduced contractility. We tested this hypothesis with the outlined model. It was found that neurotransmitter release over larger volumes resulted in lower force generation and markedly smaller ISMC contractions. These results suggest that increased distance across the neuromuscular junctions in intestinal edema is able to explain the development of ileus in such patients, lending credence to the current hypothesis.

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## G-DES: An Efficient Software For Microbial Gene-Level Diversity Estimation

Microbial genomes are dynamic; they frequently undergo different events, such as deletions, insertions or mutations, which change the sequence of genes and intergenic regions. These physical processes can induce genomic diversity in a microbial population. Advances in sequencing methods have increased our understanding of the structure and content of genomes. Previously, genomic differences were categorized in terms of the frequency of occurrence of gene variants (known as alleles). The analysis of changes in allele frequency is the foundation of population genetics. However, now, genomic differences can be measured in terms of difference in gene composition across a genome (rather than nucleotide differences between genes).Thus, there is an increasing need to quantify this "genomic variability" within a species.

The core and pan genome concepts have been proposed as one way to quantify genomic diversity within a group of organisms, e.g., within a species or genus[1]. The core genome is the set of genes found in every organism within a group. The pan genome is the set of all genes found within organisms of a group, including core genes and genes which appear in a fraction of genomes. Multiple attempts have been made to estimate the size of pan and core genomes in hopes of quantifying openness and closedness of a particular set of genomes to gene variation. Recent advances in the field pointed out that pan and core genome sizes are not robust to sampling and thus an alternative robust metric, **"genomic fluidity"** was proposed which can summarize the difference in gene content between genomes of closely related bacteria[2]. Genomic fluidity can be computed for a small number of sequenced genomes and can be used as a comparative metric between groups of closely related isolates. However, other forms of variation can also be measured, such as gene frequency distributions and the scaling of sample core and pan genome sizes. Hence, the scope of this project is to develop a microbial Gene-level Diversity Estimation Software (G-DES) to quantify microbial gene diversity in terms of two diversity metrics:

a. **Genomic fluidity**, which is defined as the ratio of unique gene clusters to the sum of gene clusters in pairs of genomes.

b. **Gene frequency distributions** which are defined as the frequency of genomes in which a particular gene occurs.

These two indices of gene diversity have the potential to enhance our understanding of gene compositional dynamics within individuals of the same species.

G-DES estimates the gene compositional differences between genomes of the same bacterial species and quantifies them by the two metrics given above. It is implemented as a collection of Perl modules. Usability is achieved by a GUI front-end giving access to all parameters. The only dependencies of the software will be Glimmer 3.0, NCBI Blast 2.2.25 and Bio-Perl 1.6.9. G-DES will then be tested against publicly available bacterial genome sequences. We utilize G-DES to quantify genomic composition within bacterial pathogens using hundreds of completely sequenced genomes.

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# Use of Lifespan-Shortening *Wolbachia* to Control Dengue Fever: Demographic Factors

Dengue fever has been recognized in over 100 countries and 2.5 billion people live in areas where dengue is endemic. It is currently a serious arthropod-borne disease, affecting around 50 million people worldwide every year. As there is no vaccine, prevention is approached by reducing the number of mosquitoes and limiting exposure to bites. However, none of these methods can effectively reduce its transmission.

Dengue fever requires a relatively long extrinsic incubation period in its mosquito vector *Aedes aegypti* before transmission to a new human host, so the life expectation of infectious vectors strongly influences the spread of the disease. The bacterium *Wolbachia* greatly shortens the lifespan of *A. aegypti* and reduces the transmission of dengue viruses. Some previous models have incorporated the effect of *Wolbachia* on mosquito lifespan and reducing disease transmission, but none of them have combined the spread of *Wolbachia* in mosquito population with an SEIR model of dengue fever. My current research focuses on a new SEIR model that explores the effect of *Wolbachia* on humans, using numerical solutions to investigate demographic factors that influence basic reproductive number and equilibrium prevalence. The persistence of the dengue fever sensitively depends on the mosquito survival profile. We studied the relationship among the number of *Wolbachia*-infected mosquitoes, the mosquito mortality rate, and the number of infectious humans at equilibrium. We found that the disease can be eliminated under certain circumstances.

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## Dynamical Systems Modeling of the Cold Shock Response in *Saccharomyces cerevisiae*

In this poster, we describe our investigations into the dynamics of gene regulatory networks governing the response of budding yeast (*Saccharomyces cerevisiae*) to cold shock. Previously in the lab, DNA microarray technology was used to measure the effect of cold shock on gene expression. The wild type strain BY4741 and strains deleted for the genes that encode the Cin5, Gln3, Hmo1, and Zap1 transcription factors were harvested during early log phase at 30ºC ($t_0$) and after being subjected to cold shock at 13ºC for 15, 30, or 60 minutes followed by recovery at 30ºC for an additional 30 or 60 minutes. Four to five replicates were performed for each strain and time point. Total RNA was purified from each sample, labeled and hybridized to a total of 103 DNA microarrays. Each cold shock or recovery time point (labeled with Cy5) was competitively hybridized with labeled aRNA from the $t_0$ time point (labeled with Cy3). The orientation of the Cy3 and Cy5 dyes was swapped for two of the replicates for each strain.

Within-chip spatial and intensity biases present in the microarray data arising from dye intensity and print tip variation were corrected using Loess normalization. To correct for chip-to-chip variation, median absolute deviation scaling was also performed. The R Statistical computing environment and the limma package were used for these normalizations.

Changes in gene expression due to cold shock are controlled by a network of transcription factors which bind to regulatory DNA sequences. A gene regulatory network for the cold shock response was constructed from a set of transcription factors that are known to regulate each other as documented in the YEASTRACT database. Transcription factors were included in the network if their target genes were enriched in a list of genes that had significant differential expression in the microarray data or if there was other experimental evidence suggesting their involvement in the cold shock response. The resulting network consists of 21 nodes, each of which represent the gene, the mRNA, and the protein transcription factor it encodes, assuming that a gene is translated into protein as soon as it is transcribed. These nodes are connected by 50 directed edges which represent the regulatory relationships, either activation or repression, depending on the sign of the weight of the regulatory effect.

Expression of each gene in the network was modeled by a nonlinear differential equation describing the change in expression over time as the difference between the production rate and degradation rate. The production is modeled by a sigmoid function which takes into account a weight parameter which describes the influence (activation or repression) of each transcription factor that regulates that gene, the expression level of the gene at a given time, and a constant that determines the position of the expression threshold. The degradation rates in the model were taken from Belle *et al.* (2006, *PNAS* 103: 13004–13009). The ode45 function in MATLAB was used to solve the differential equation model given a set of initial conditions. The fmincon function in MATLAB compared the model to the microarray data to find optimized weights and threshold constants by a nonlinear least squares fit criterion. We present results comparing fits derived from analyses of each strain individually with results fitting all strains simultaneously. In both of these approaches, the deletion strains are modeled by removing the gene from the dynamical system.

This work was supported by NSF award 0921038 (KDD, BGF, KS) and the McLaughlin Chair of Biology (KDD, NAR).

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## Stochastic modeling of bacterial chromosome segregation

Eukaryotic cells use complex machineries during division in order to ensure the faithful segregation of their DNA to the daughter cells. In prokaryotic cells, similar active segregation mechanisms are beginning to emerge. Here we present stochastic mathematical models that describe the segregation machinery of *Caulobacter crescentus*. In this bacterium, depolymerizing filamentous proteins have been implicated in fueling and directing the movement of the replicated circular chromosome copies. We show that the spatial organization of the filaments and their dynamics can have unexpected effects on the chromosome movement mediated by processive binding of depolymerization-inducing proteins. Finally, we discuss a continuum PDE model that captures the movement of DNA as well as the cytoplasmic dynamics of regulatory proteins for this bacterium. We conclude by highlighting similarities in division mechanics between these bacterial cells and higher eukaryotic cells.

**Daniel Sindelar**, and James D. Benson, Northern Illinois University, Dekalb, Il, USA

## Modeling Mass Transport During Cell Cryopreservation and Determining Parameters for Cellular Lysis Upon Thawing

Cells are cryopreserved in concentrated media that becomes even more so as temperatures are reduced and extracellular ice forms. If cooling rates are slow, the cells remain in equilibrium with the extracellular environment until they are plunged into liquid nitrogen. It often is ideal to warm extremely rapidly, melting the surrounding media as quickly as possible. This results in cells that are relatively concentrated compared to their surrounding media. This concentration gradient drives water into the cells, causing them to swell and, potentially, rupture. This phenomenon is known to occur but has not been well explored and documented mathematically. Here we use a differential equation model for mass transport in cells to explore and understand the conditions under which this damage will and will not occur. We determine the appropriate model and solution technique, and analyze results in the context of the original application.

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## Sequential modeling of the effects of mass drug treatments on Anopheline-mediated lymphatic filariasis infection in Papua New Guinea

Inherent bioecological complexity in transmission dynamics and parameter uncertainty complicate the prediction of extinction endpoints for complicated parasitic systems, such as the vector-borne macroparasitic disease, lymphatic filariasis (LF). One source of this difficulty is the limited quantity and quality of data used to develop and parameterize numerical models of parasite transmission, implying that model fitting methods that can be used to sequentially update or refine initial parameter estimates will be essential for reducing extant uncertainty regarding values of transmission/infection endpoint/breakpoints within and between endemic localities.

Here, we extend a newly developed numerical modelling and Bayesian Melding calibration framework in order to fit our previously developed deterministic LF transmission model to human age-infection prevalence data recorded from several village communities in Papua New Guinea that underwent annual mass drug treatments. Specifically, we examine: 1) whether transmission controlling parameters remained stable (from baseline estimates) in the face of the specific interventions implemented in each of these communities, 2) if it was possible to use the model fits from each intervention period to reliably perform backward extrapolations to reconstruct baseline age-infection patterns, 3) whether it was possible to use post-intervention infection data to estimate LF transmission/infection endpoints consistent with those estimated using baseline only data, and 4) if such a modelling and fitting framework can allow better estimates of drug treatment-related parameters.

We show that transmission parameters obtained by fitting the model to data from baseline versus each intervention period remain stable throughout the whole study period. This result enabled us to reliably reconstruct the observed baseline data in each community. Estimates of worm breakpoint values from both direct as well as back-fits to baseline data also showed little variation. The employed updating procedure showed a shift towards higher and less variable values for the worm but not the microfilaria killing parameter.

This work demonstrates that biological parameters governing the transmission process of LF in endemic communities may not change appreciably during an intervention period. This result implies that endpoint values for this disease, which is currently being targeted for global elimination, can be successfully estimated by model fitting of post-intervention monitoring data, if the drug regimen parameters and population coverage values, along with information on the frequency and number of treatments, are available for any given endemic community.

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## Spatially inhomogeneous bacterial clusters in weak shear flow

The bacteriaemial cluster dynamics has many novel properties, which widely differ from the traditional soft condensed matter systems and arise from a rich spectrum of non-equilibrium behavior: flocking, chemotaxis and bioconvection. In this talk we will detail how to derive a hydrodynamic model for swarming clusters with particles of an arbitrary shape, moving in a 3-dimensional space inside a viscous solvent and in a sufficiently dilute suspension limit. The model is then restricted to particles with ellipsoidal geometry to quantify the interplay of the long-range excluded volume and the short-range self-propulsion effects. The expression for the constitutive stresses, relating the kinetic theory with the momentum transport equations, are derived using a combination of the virtual work principle (for extra elastic stresses) and symmetry arguments (for active stresses). We then provide preliminary results of these cluster flows, moving in a weak shear.

**A mathematical model of Bieber Fever: The most infectious disease of our time?**

Val Tweedle and **Robert Smith?**
The University of Ottawa

Abstract: Recently, an outbreak of Bieber Fever has blossomed into a full pandemic, primarily among our youth. This disease is highly infectious between individuals and is also subject to external media pressure, further strengthening the infection. Symptoms include time-wasting, excessive purchasing of useless merchandise and uncontrollable crying and/or screaming. We develop a mathematical model to describe the spread of Bieber Fever, whereby individuals can be susceptible, Bieber-infected or bored of Bieber. We analyse the model in both the presence and the absence of media, and show that it has a basic reproductive ratio of 24, making it perhaps the most infectious disease of our time. In the absence of media, Bieber Fever can still propagate. However, when media effects are included, Bieber Fever can reach extraordinary heights. Even an outbreak of Bieber Fever that would otherwise burn out (driven by fans becoming bored within two weeks) can still be sustained if media events are staggered. Negative media can rein in oversaturation, but continuous negative media (the Lindsay Lohan effect) is the only way to end Bieber Fever. It follows that tabloid journalism may be our last, best hope against this fast-moving and highly infectious disease. Otherwise, our nation's children may be in a great deal of trouble.

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## Stoichiometry Driven Patch Foraging: A Nutrient Explicit Dynamic State-Variable Model

Theoretical biologists studying foraging behavior have long ignored nutrient specific models; instead most have utilized the energetics paradigm, black-boxing the specifics of the organism's resources. The integration of nutritional ecology, ecological stoichiometry, and optimal foraging theory is an emerging area of study that may lead to significant insights in all of these areas. In this model we explore the connection between predation risk, nutrient acquisition and allocation using a dynamic state-variable model. Organisms show temporal variation in their elemental construct throughout their life times, this is because they perform different biological functions at different stages in their life history. It follows that in order to achieve these different constructs, organisms will need to alter the nutrients that they intake. How organisms obtain and allocate resources may also depend on their state, such as the individual's fat reserves, body size, or shell size.

In order to understand how a nutrient explicit approach may alter our understanding of state-dependent behavior we have constructed a model based on the life history of physid freshwater snails (Physidae sp.). This system allows us to separate nutrients that are used for body growth and shell growth. Snails that forage in phosphorus-rich patches achieve faster body-growth, where a snail's clutch size is dependent on their body mass. Individuals foraging in calcium-rich patches may accomplish faster shell-growth, which decreases an individual's predation risk. We use a dynamic state-variable model to see how this would affect foraging on patches with differing phosphorus to calcium ratios, and how initial body sizes, shell sizes and predation risk influence their foraging behavior and morphology over their lifetime.

Previous work in this area has shown that initial state variables can influence behavior and future state variables in two different ways. The "asset protection principle" predicts a negative feedback loop between initial states through time, where individuals with a higher reproductive value (based upon some of the state variables), would be more risk averse because they have more fitness assets built up that they could lose. Individuals with lower reproductive value are predicted to use more risky behavior because they have less to lose. The outcome over time is that individuals all converge on the similar state values. However, a second phenomenon of state-dependent predation risk can work as a positive feedback loop, where small differences in initial state result in diverging state values. The model that we put forth investigates whether integrating nutrients that affect different state-variables that perform different biological functions can produce both phenomena.

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## Randomness in the Expression of Genes

The process by which the genetic code comes to life is a fundamentally stochastic process. In order to begin to quantify this randomness, this work models transcription using a population density approach. In the model, a single gene of interest fluctuates stochastically between an inactive state, in which transcription cannot occur, and an active state, in which discrete transcription events occur; and the individual mRNA molecules are degraded stochastically in an independent manner. The random dwell times in the inactive and active states are independent random variables drawn from any specified distributions. Previously, this sort of model with exponential dwell times has been successful in explaining experimental estimates of the distribution of random mRNA copy number within a population of isogenic cells.

I will present efficient numerical methods for computing steady-state mRNA distributions, an analytic formula for the mRNA autocovariance function, and a procedure for model identification based on laboratory data. It will be shown that the autocovariance function can, in some situations, be used to disambiguate gene switching models. Temporal data beyond the autocovariance function is required in general to characterize gene switching. It is hoped that these theoretical advancements will lead to a better understanding of stochastic gene expression, in theory and experimentally.

**Magdalena Stolarska**, University of St. Thomas, St. Paul, MN, USA

## Mathematical models of mechanical aspects of cell motility and cell-substrate interaction

Mechanical interactions between a cell and the substrate are vital for cell migration and signaling. It has been shown experimentally that cell-substrate mechanical interactions affect signal transduction in processes such as focal adhesion growth and shrinkage, stress fiber formation, and the cyclic extension and contraction phases of certain motile cells, such as *Dictyostelium discoidium*.

In the talk, I will present two mathematical models aimed at understanding the mechanical stresses that occur during cell motility and the effect of cell-substrate interaction on these intracellular stresses. The first model treats the cell as a two-dimensional hypoelastic continuum that is moving over a two-dimensional elastic substrate. Focal adhesions are modeled as collections of discrete elastic springs that can break and reform, and cytoskeletal organizations driving cell movement are captured by an empirical active deformation tensor. A finite element implementation of the model of cell and substrate deformation is coupled to the equations governing the dynamics of the adhesions. The resulting simulations are used to better understand the oscillatory nature of amoeboid cell motility. In a slightly different context, we also couple the model for the intracellular mechanical interactions to a reaction diffusion model of the transport of plaque proteins that are required for dynamic reorganization of focal adhesions. The goal here is to illustrate how mechanics can affect biochemical kinetics within the cell, and in particular how mechanical interactions lead to the formation of observed focal adhesion patterns on the cell-substrate interface.

In the second mathematical model, we consider a cell moving through a two-dimensional slice of a three dimensional collagen network. In this case, based on the work of Yang and coworkers (2008), the cell is modeled as a fluid enclosed in an elastic membrane, and the collagen network is modeled as series of deformable beams. Governing equations for an elastica (an inextensible, highly deformable rod) are used to model collagen fiber deformation, and the deformation of the cell membrane as well as cell-collagen interaction is tracked using the level set method. Preliminary numerical implementation of this model are used to understand how the mechanical properties of the collagen affect the morphology of the cell moving through it. While the two models presented in this talk are qualitatively different, their overall purpose is to allow us to gain a better understanding of how mechanical interaction with the environment through which a single cell moves affects its movement.

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## Mathematical Model for Mountain Pine Beetle Spread and Impacts of Park Management Strategies

The current Mountain Pine Beetle (MPB, *Dendroctonius ponderosae*) outbreak has reached the highest population levels in recorded history, particularly in British Columbia. The spread and intensity of the outbreak has been largely attributed to fire suppression practices and climate change. Parks Canada has spent significant funds on management actions aimed at stemming the infestation, but the effectiveness of these measures is mostly unknown, and is difficult to determine with field work alone. Mathematical modelling is a useful tool in this work, as it can be used to investigate the effect of different management strategies without damage to the landscape or economy. My research focuses on evaluating management strategies implemented in Banff National Park (NP).

I have developed a diffusion-reaction-chemotaxis model describing MPB population dynamics and dispersal. This model incorporates the interaction between MPB, susceptible Lodgepole Pine trees, and the pheromones produced by MPB. This spatially explicit model describes the summer flight period of the MPB. A set of discrete difference equations is used to model the overwinter reproduction of MPB and the impact of MPB on the suscetible landscape. This model is run over multiple years to show the progression of MPB attack over time.

The management actions implemented in Banff NP are prescribed burning and baiting and green-attack tree removal. The prescribed burning removes possible habitat for MPB but can not be used as a tool to kill the MPB directly. Baiting is used to focus MPB attacks in an area and then intensive land surveys would be completed to determine the recently attacked trees in the fall. Since the trees attacked by MPB have not developed a red-top yet,the trees are still green. These green-attack trees are removed and burned to prevent spread of MPB.

Management actions are simulated over multiple years and the results of these simulations inform when each particular management action is the most effective at stemming the infestation of MPB.

**Wanda Strychalski**, University of California, Davis, CA, USA
Robert D. Guy, University of California, Davis, CA, USA

## Computational explorations of cellular blebbing

Blebbing occurs when the cytoskeleton detaches from the cell membrane, resulting in the pressure-driven flow of cytosol towards the area of detachment and the local expansion of the cell membrane. Recent interest has focused on cells that use blebbing for migrating through three dimensional fibrous matrices. In particular, metastatic cancer cells have been shown to use blebs for motility. A dynamic computational model of the cell is presented that includes mechanics of and the interactions between the intracellular fluid, the actin cortex, the cell membrane, and the cytoskeleton. The computational model is used to explore the relative roles of cytoplasmic viscosity, intracellular drag, and cytoplasmic elasticity on bleb expansion dynamics. The model is also used to investigate outstanding hypotheses on intracellular pressure propagation.

**Jillian Stupiansky**, University of Florida, Gainesville, FL, USA
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## An Introduction to Citrus Greening and a Host-Vector Model with Roguing

Huanglongbing (HLB), commonly known as citrus greening disease, is a vector-transmitted bacterial disease that is significantly impacting the citrus industry in Florida and poses a great risk to the remaining citrus-producing regions of the United States. This is a very important issue because Florida is the nation's largest citrus producer and the second largest producer of orange juice in the world. A recent study by the University of Florida's Institute of Food and Agricultural Sciences estimates that from 2006 to 2011 citrus greening has caused $3.63 billion in lost revenue and over 6,000 lost jobs in the state. The five-year production level for orange juice is estimated to be 1.7 billion gallons less than projected. In addition to Florida, the presence of HLB has also been detected in other southeastern states as well as in Texas and California.

An insect known as the Asian citrus psyllid, Diaphorina citri, carries the organism that causes citrus greening, Candidatus Liberibacter asiaticus (Las). An infected psyllid carries the bacteria in its saliva and infects a healthy tree when it feeds. Similarly, a healthy psyllid can get the bacteria from a diseased tree. Observations suggest that once a tree becomes infected, it may remain asymptomatic for six months to six years, contributing to the difficulty in controlling the disease. While an adult psyllid can usually only fly a mile, citrus greening has been able to spread throughout almost the entire state of Florida due to the transportation of infected citrus stock by discount stores. Recent findings also support the idea that the disease is transmitted transovarially and sexually amongst the psyllid population. This would help to explain why the disease has spread so rapidly.

Multiple control strategies have been used, such as applying insecticides to groves and administering antibiotics to affected trees. However, in addition to being very costly, none of these techniques have been completely effective so far. Another method is to rogue (or remove) an infected tree and replant a healthy tree in its place. We have developed a mathematical model for the host and vector populations within a single grove of trees which uniquely incorporates roguing as a control strategy. Our model includes four stages for the trees (susceptible, infected but asymptomatic, infected and symptomatic, and dead) and two vector stages (susceptible and infected). Roguing is incorporated in both the symptomatic and dead states, and then the replanted trees can enter either the healthy or asymptomatic states.

Our analysis of the model includes finding the equilibria and calculating a condition for existence of positive endemic equilibria. We also calculate the basic reproduction number $R_0$ using the next-generation matrix method. Since there are many different definitions of $R_0$, we show the equivalence of our mathematical basic reproduction number to one with a biological interpretation. Finally, we look at a variation on the term that represents transmission of the disease between trees and vectors. If either the psyllids or trees are considered as a limiting factor, the new transmission term yields only slight changes in our $R_0$ value.

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## Effect of Biofilm Deformation on Detachment, Mass transfer and Growth

Bacterial biofilms are microbes growing on surfaces and wetted interfaces in aqueous environments.They form when the cells in the fluid attach themselves to the surface and start to producing an extracellular polymeric matrix, in which the growing bacteria cells embed themselves. This gel like layer protects the embedded bacteria from harmful environmental effects such as anti-microbials and provides mechanical stability to the biofilm to resist detachment.

The mechanical response of the biofilm depends not only on the material property of the biofilm but also on the shape and morphology of biofilm-flow interface. Rheology experiments done over the years by different groups on biofilms grown under different conditions using different measurement techniques have provided differing description of the biofilm response (elastic, viscoelastic solid, viscoelastic fluid) with material parameter values varying over a wide range. Most of the current mathematical models studying biofilm growth and detachment do not account for the deformation of biofilm or do so in an adhoc way to avoid numerical difficulties arising from the fluid structure interaction problem or do not make use of material property values measured from experiments. In our talk, we will present the results from our simulations (1-D as well as 2-D) where we explored how the deformation of the biofilm resulting from different material description affects the detachment forces acting on the biofilm as well as the mass transfer to the biofilm.

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## Size Structured Model for Tissue Cyst Growth of *Toxoplasma gondii*

When a host becomes infected with *Toxoplasma gondii*, the host undergoes acute infection for several weeks. Once acute infection is complete, the parasites migrate mostly in the brain and some muscle tissue and reach a chronic steady-state of the number of cysts observed. The chronic steady-state is typically reached by 3 months after the initial infection. There are two competing phenomenon that control cyst growth during chronic infection. Parasites naturally replicate within a host cell, and thus the volume of the cyst increases as the parasites replicate. On the other hand, cysts can burst, which release parasites that are then free to infect healthy host cells, thereby restarting the cycle of cyst growth. This process of bursting is mediated by a natural bursting rate and by an immune response suppression of bursting. The two bursting factors, natural and immune response, are represented by a single function. By proposing a general cyst-size distribution model that takes into account different growth and bursting functions, a maximum likelihood approach to fit the model to the existing data is used.

This research carries three components: existing data analysis, hypothesizing various size-growth and bursting functions for tissue cysts, and model selection and validation. Existing data is analyzed by finding the appropriate time to quantify the dynamics of the cyst-size distribution as a steady-state through an appropriate mean-difference p-test. The size-growth functions that may be used to fit the data are of the following forms: constant, linear, or exponential. The possible bursting functions can be in the form of a linear, exponential, type II, or type III function. The above size-growth and bursting functions are analyzed within a time-size partial differential equation at steady state to find the best match to the available cyst-size distribution data.

The results of the model analysis show that by using the AIC as a criteria for suggesting good and bad fits of the growth and bursting functions in the size-growth model, it is possible to show that the growth and bursting functions are best described by one of several cases. The best cases appear to have a nearly constant (i.e. constant or exponential with a very slight decrease from the initial value over the range of observable data) size-growth rate function combined with a type II or type III bursting function. This suggests that over the typical observable range of sizes, the size growth function that best describes the data is nearly constant and the bursting function that best describes the data is a type II or type III response function. The function with the best AIC is a type III bursting function that is slowest of the three type III cases (when paired with the three size growth functions) in reaching the asymptote of the predicted magnitude.

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## Towards an Understanding of SHAPE-directed RNA Structure Prediction Accuracy

RNA secondary structure prediction remains an open problem in computational biology. Data from recently emerging high-throughput structure probing technologies, such as the SHAPE method, have been used in the framework of thermodynamic optimization to predict RNA secondary structure. We investigate the factors influencing the accuracy of SHAPE data-directed predictions via stochastic simulations. We find that the accuracy of data-directed predictions is broadly correlated with the accuracy of undirected predictions. Our analysis also indicates that it is possible to broadly estimate the prediction accuracy of a sequence by the similarity between the undirected and data-directed structures. At the level of individual basepairs, we find that those common to a data-directed prediction and the undirected structure are more likely to be correct than base pairs that are only in the undirected structure. Finally, we explore the potential of constraints in the form auxiliary data to improve prediction accuracy.

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## Intermittent transitions between rich and poor communities in evolutionarily constructed food webs

The emergence and maintenance of biodiversity is one of the most fundamental challenges in ecology. Recent studies have demonstrated that evolutionary processes affecting interactions within and among species can be faster than previously thought, that the effect of such evolution on the underlying ecology can be appreciable, and that this ecology can in turn affect, through eco-evolutionary feedback, the shape of the fitness landscapes driving adaptive evolutionary change. While several models have been proposed to investigate the emergence and maintenance of community structures, most of these are based on separating the timescales of ecology (describing changes in species abundances) and evolution (describing changes in species traits).

Here, we develop an individual-based model that does not impose an artificial separation of ecological and evolutionary timescales. Our model considers the evolution of two quantitative traits expressed and inherited by each individual, called foraging and vulnerability traits, that control trophic interactions and interference competition between individuals. Specifically, the foraging intensity of one individual with respect to another is determined by the similarity between the former's foraging trait and the latter's vulnerability trait. Analogously, the intensity of interference competition between two individuals is determined by the similarity of their foraging traits. Population dynamics are represented stochastically, as an individual-based birth-death process, and also evolution is represented stochastically, resulting from rare and small mutational steps in trait values potentially occurring at birth.

Analyzing our model, we (1) observe the robust and recurrent emergence of two different metastable community states, one in which producers are dominating the community and an alternative one in which producers are coexisting with consumers. We also (2) demonstrate a distinctive pattern of intermittent transitions between those two metastable states and (3) explain the eco-evolutionary mechanisms underpinning this transition process. In conclusion, we suggest that evolutionarily induced transitions between metastable community states, through community breakdown and subsequent rebound, could be important for understanding the long-term dynamics of empirical patterns of biological diversity.

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## Not all Parameters Matter: Local and Global Sensitivity Analysis applied to Phage Lambda Lysis/Lysogeny Models

Mathematical models are increasingly prevalent in systems biology with the goal of providing predictions and insight that may be less accessible by intuition alone. However, analysis of these models can be challenging because they are often defined by a large number of parameters and non-linear interactions between components. While brute-force numerical simulations have been used for analyzing models, the large-variation in parameters and the very large parameter space make the analysis difficult.

Here we consider methods to rationally explore model dynamics using recent innovations in the area of sensitivity analysis (SA). In particular, we utilize a recent technique called 'Sloppy-stiff' SA method to quantify how changes in parameter values affect model output[1]. This method is realized through calculating partial derivatives of a cost function dependent on the output dynamics at a local point in parameter space. We extend the local analysis to look globally by sampling in a large range of biologically feasible parameter space to demonstrate that results from any particular local SA may not match the global trends. Looking globally gives us a distribution of the importance of parameters in the space.

To illustrate how different parameters differentially contribute to the overall dynamics of models, we apply SA to models of the lysis/lysogeny decision for phage Lambda infecting *E. coli*. The underlying gene regulatory network is believed to be bistable corresponding to two different phenomenological outcomes. After infection there can either be an immediate production and release of new viruses through a bursting of the bacterial cell (lysis), or the viral DNA can incorporate itself with the bacterial DNA and lay dormant (lysogeny) until a more favorable time to undergo lysis. Experiments have demonstrated that the lysogenic outcome is more likely when more phages infect a given cell[2,3] and lysogeny is also more likely with decreasing cell volume[4]. Theory suggests that this change in behavior is mediated by a change in viral genome concentration[5] along with stochastic effects[3]. However, the relationship between network parameters and cell fate outcome remains unresolved. Here, we utilize SA to evaluate candidate models of cell fate determination and determine the relative importance of parameters to cell fate outcome.

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## The role of motility and nutrients in bacterial competition and colony formation

Bacterial competition and colony formation are an important component in many practical applications such as plant roots colonization and medicine (especially in dental clinics). Motility is a pivotal bacterial trait for the successful colonization of plant roots. Bacterial motility has two types of mechanisms — directed movement (chemotaxis) and undirected movement. Motivated by a series of petri dish experiments, we study undirected bacterial movement which is rarely considered in literature. To study bacterial competition and colony formation in a petri dish, we modify and extend the model used in Wei et al.(2011) to obtain a group of more general and realistic PDE models. We explicitly consider the nutrients and incorporate two bacterial strains characterized by motility. We use different nutrient media such as agar and liquid in the theoretical framework to discuss the results of competition and colony formation. The consistency of our numerical simulations and experimental data illustrates the existence of undirected motility in bacteria. In agar, the motile strain has higher total density while in liquid, the immotile strain has a similar total density. When we place two drops of these bacterial strains around the middle of the petri dish, we find that 1) in agar, after half a day, the density of the motile strain is high on the boundary of the petri dish; in contrast the density of the immotile strain is high in the middle of the petri dish; 2) in liquid, bacterial motility is not that important because liquid nutrients move almost infinitely fast compared to bacterial movement. Furthermore, we find that in agar as bacterial motility increases, the extinction time of the motile bacteria decreases without competition but increases in competition. When the nutrient media varies from agar to liquid, the extinction time of the motile strain decreases while the extinction time of the immotile strain increases, and the total density ratio of motile to immotile decreases dramatically. In addition, we show the existence of traveling-wave solutions mathematically and numerically.

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## Modelling quantitative genetics: how to be genetically explicit

There are two main approaches to modelling genetic evolution. On the one hand, we can represent alleles as discrete values. On the other hand, we can represent alleles as a continuum of values. Even if both representations are used in individual-based simulations to study evolutionary processes, the dynamics that they generate can be different for the same problem. The difference in variance is the most problematic. We are presenting a comparative analysis of the discrete versus continuous allele representation in evolutionary individual-based simulations. We compare both approaches to theoretical predictions, such as mutation-selection balance, different contexts and effect of the number of loci, selection strength and mutation effect size.

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Giles Hooker, Cornell University, Ithaca, NY, USA

## Control theoretic methods for experimental design in Partially Observed Markov Decision Processes

How do we most effectively use controls within the framework of Partially Observed Markov Decision Processes (POMDP) so as to provide data that is most informative about parameters of interest? This talk attempts to give a partial answer to this question. Methods from Markov decision process, especially dynamic programming, will be introduced and then used in an algorithm to maximize a relevant Fisher Information. The algorithm will then be applied to a POMDP example. The methods developed can also be applied to stochastic dynamic systems, by suitable discretization, and we consequently show what control policies look like in the Morris-Lecar Neuron model, and some simulation results will be presented. We show how parameter dependence within these methods can be dealt with by the use of priors, and by updating policies online.

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## Mathematical Modeling of Tumor Dynamics and Radiotherapy for Early Glioma

Glioblastomas are very aggressive brain tumors with a poor prognosis. These highly vascular and invasive tumors exhibit a high degree of cellular heterogeneity that accounts for their resistance to standard therapies. To estimate the amount of cellular destruction through radiotherapy, we use mathematical models such as the linear-quadratic model. In this work the growth of glioma is simulated in conjunction with the effects of radiotherapy on a microscopic scale. Furthermore, we consider the variability of the radiation sensitivity of individual cells as a function of the cell cycle phase.

We propose a hybrid approach for modeling tumor progression on a cellular scale. The spatio-temporal model consists of reactiondiffusion equations that describe interactions between cancer cells and the microenvironment. The movement of tumor cells, the distribution of the nutrients and the density of the extracellular matrix is covered by partial differential equations. Additionally, the cell cycle is incorporated to allow for a more accurate modeling of biological processes. The simulation of radiotherapy is based on the linear-quadratic model. Here, the effects of irradiation are influenced by the administrated dose and two parameters representing the radiosensitivity of tissue with respect to the cell cycle.

A qualitative evaluation of first results shows an initial exponential growth of the tumor. During therapy, after each fraction of radiation the population of tumor cells decreases steadily. During treatment breaks, an increase of the population can be observed. The model was also used to study the effects of the radiation dose and a direct dependence between the dose and the tumor cells can be observed.

The simulations depict plausible results for both, the progression of tumor and the effect of radiotherapy on individual cells. By introducing molecular and/or macroscopic components into this model, a multiscale approach describing the effects of radiotherapy is possible.

## Insights gained from mathematical modeling of HER2 positive breast cancer

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Abstract: As the understanding of cellular regulatory networks grows, system dynamics and behaviors resulting from feedback effects have proven to be sufficiently complex so as to prevent intuitive understanding. Mathematical modeling in engineering has traditionally sought to extrapolate from existing information and underlying principles to create complex descriptions of various systems, which could be analyzed or simulated, and from which further abstractions could be made. However, in studying biological systems, often only incomplete abstracted hypotheses exist to explain observed complex patterning and functions. The challenge has become to show that enough of a network is understood to explain the behavior of the system. Mathematical modeling must simultaneously characterize the complex and nonintuitive behavior of a network, while revealing deficiencies in the model and suggesting new experimental directions. In this talk, we describe the process of modeling treated regulatory networks in breast cancer. We demonstrate the use of the mathematical models in both understanding the system, and in suggesting new treatments. The talk will conclude with experimental results on HER2 positive cell lines. This is joint work with Soulaiman Itani, Young Hwan Chang, Jim Korkola, and Joe Gray.

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## Modeling Cortical Folding with a Growing Domain Turing System

The brain is one of nature's greatest mysteries, and the cerebral cortex is one of the brain's most striking features. The cerebral cortex is intricately folded into gyri (hills) and sulci (valleys). The folding patterns of these gyri and sulci are unique, both across species and across individuals within a species, much like a fingerprint. Little is understood about how cortical folds form and why they are located where they are. Current biological models of the underlying processes behind cortical folding fall into two main categories; some models highlight the importance of chemical interactions, while others place the primary emphasis on mechanical forces such as tension. We have developed a spatio-temporal mathematical model of cortical folding on a growing domain, expanding upon previous mathematical research on cortical folding conducted using a static domain. A growing domain model of cortical folding may be more realistic than the previous static domain model since it incorporates the growth that inherently occurs as the brain develops. Our model illustrates the importance of including growth in a model of cortical folding and can be utilized to explain certain human diseases of cortical folding. It can help investigate an area of neuroscience where it is difficult to perform human experiments.

Our model utilizes a Turing reaction-diffusion system on an exponentially growing domain. Turing reaction-diffusion systems were originally developed to describe formation of chemical gradient patterns on the developing embryo, and have since been used to model pattern formation associated with various developmental biology phenomena, including leopard spots, zebra stripes, and many more. Turing systems are typically two-equation activator-inhibitor systems that, when certain criteria are satisfied, cause spatially homogeneous systems to generate spatially inhomogeneous patterns. We use the Barrio-Varea-Maini reaction kinetics with parameters that favor striped pattern formation in our Turing system model.

The Turing system in our model can be applied to a growing domain in any of the eleven coordinate systems upon which the Helmholtz equation is separable. This gives the model great flexibility and the potential to be used for mathematical modeling on a geometrically diverse group of domains. To apply the model to cortical folding, we select an exponentially growing prolate spheroid, which approximates the shape of the lateral ventricle (LV) during early stages of cortical development. A prolate spheroid is obtained by rotating an ellipse around its major axis; the focal distance of the spheroid is determined by the length of its semimajor and semiminor axes. In our model, the focal distance of the prolate spheroid grows exponentially so that the spheroid's shape is preserved as it grows isotropically. The Intermediate Progenitor Model (IPM) of cortical folding states that regional patterning of self-amplification of intermediate progenitor cells (IPCs) in the subventricular zone (SVZ) of the LV corresponds with the formation of gyri and sulci. As self-amplification of IPCs is genetically controlled via chemical gradients, a Turing system is a logical choice to create a mathematical representation of the IPM. Our Turing system model uses the exponentially growing prolate spheroid to represent the LV and its surface to represent the SVZ.

Using numerical simulations to compare and contrast patterns generated by our growing prolate spheroid Turing system with those generated by a static prolate spheroid Turing system, we show that the addition of growth causes a significant change in system behavior. While it is well-documented that a static domain Turing system converges to a final pattern like a developing photograph, a growing domain Turing system produces transient patterns that constantly evolve from one pattern to another. We also observe that increasing the exponential growth rate in our system increases the number of stripes in the generated pattern, which can be interpreted as in increase in the number of cortical folds. This result may help explain a form of polymicrogyria (a cortical folding malformation characterized by an excessive number of small gyri) which occurs with hydrocephalus (a build-up of cerebrospinal fluid in the brain causing the LVs to increase in size). Our model could shed more light on the underlying mechanics behind cortical folding and diseases of folding as well as the role of growth in these processes.

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## Structural basis for dynein motor domain coordination

Dynein motor proteins power cellular processes, such as directed vesicle transport and cilia beating, by converting the chemical energy of Adenosine Triphosphate (ATP) into mechanical work. Cyclic functioning of the motor requires coordination of biochemical and mechanical changes in its catalytic domain. Processive hand-over-hand motion also implies an inter-domain coordination of the two heads. Despite extensive research efforts, a detailed picture of mechanochemical coordination and force generation by dynein remains controversial. One of the main challenges in elucidating a functional mechanism is the large size of the motor. Until recently, only crystal structures of isolated domains have been available. However, even recent crystallization of a full-size dynein did not offer immediate explanation for how the motor operates.

Combining available data from both structural and biochemical studies on dynein, we developed a coarse grained model of the full motor. Stochastic simulations demonstrate that the model is consistent with experimentally observed stepping behavior and suggest answers to a number of fundamental questions about dynein's mechanochemistry. The model demonstrates how a direct physical interaction between dynein's AAA+ rings can occur without disrupting movement of the heads during 8.2 nm stepping. In fact, this interaction facilitates coordination and efficiency of motor function. We demonstrate how and why dynein is capable of switching between processive forward and backward runs while maintaining a directional bias for forward stepping. Finally, we explore sources of dynein's structural flexibility and their effects on the step size distribution. Our model provides a computational framework for studying cooperative multi-motor transport and collective force generation, thus bridging dynamic phenomena on the length scales of nanometers to microns.

# A diffusion-based model to predict wild bee dispersal and survival in mixed landscapes

J.B. Wilson* R.C. Tyson†

**Abstract**

The distribution of native bees across a landscape is an important factor for pollination, conservation, and sustaintability. Pollinator distribution data is difficult and expensive to collect directly, so a mathematical model can be used to extrapolate from known local behaviours and predict large scale population behaviour. Here we present a diffusion-based model with intensive and extensive search modes for the movements of native and domestic bees in a landscape consisting of native and agricultural habitats. We investigate how native bees disperse in response to floral resource distribution and density of other bees, either wild or domestic. Exploration of both single day and season long behaviours gives comprehensive understanding of bee dispersal and resource collection. Our results suggest that the lower number of native bees observed in crops pollinated by honeybees may simply be due to the increased competition for floral resource. We also demonstrate the existence of a lower bound for the size of native habitat needed to maintain a bumblebee population servicing an agricultural crop, and investigate the effectiveness of wild bumblebee populations as pollinators of an agricultural crop.

For a single hive of bees, we derive the following model equations:

$$\frac{\partial F(x,t)}{\partial t} = \overbrace{D\nabla^2 F(x,t)}^{\text{diffusion}} + \overbrace{\gamma_1 \Delta N(x,t) S(x,t)}^{\text{conversion to foraging}} - \overbrace{\gamma_2 F(x,t)}^{\text{conversion to scouting}}, \tag{1a}$$

$$\frac{\partial S_r(x,t)}{\partial t} = \overbrace{-(A_r(x)) \cdot \nabla S_r(x,t)}^{\text{advection R and CPF}} - \overbrace{\gamma_1 \Delta N(x,t) S_r(x,t)}^{\text{conversion to foraging}} + \overbrace{\frac{1}{2}\gamma_2 F(x,t)}^{\text{conversion to scouting}}, \tag{1b}$$

$$\frac{\partial S_l(x,t)}{\partial t} = \overbrace{(A_l(x)) \cdot \nabla S_l(x,t)}^{\text{advection L and CPF}} - \overbrace{\gamma_1 \Delta N(x,t) S_l(x,t)}^{\text{conversion to foraging}} + \overbrace{\frac{1}{2}\gamma_2 F(x,t)}^{\text{conversion to scouting}}, \tag{1c}$$

$$S_T(x,t) = S_r(x,t) + S_l(x,t), \tag{1d}$$

where $F(x,t)$ is the density of foraging bees at $x$ at time $t$, $S_r(x,t)$ and $S_l(x,t)$ are the density of bees scouting right and left, respectively, and $S_T(x,t)$ is the total density of scouting bees. Bees are central place foragers, in that they must regularly return to the hive to unload the pollen and nectar collected in the field. The overall advection velocity is thus given by $A(x) = v - C_i(x)$, where $C_i(x)$ is a restoring function for scouts moving in direction $i$, that constrains their movement to within a certain radius of the hive. The function $\Delta N(x,t)$ is the change in nectar production rate at position $x$ and time $t$.

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## Actin driven membrane waves during lymphocyte activation

Spreading of cells involves large scale physical rearrangements of the actin cytoskeleton and cell membrane. The spreading of T and B-lymphocytes on antibody coated substrates mimics the formation of the immune synapse, a multi-protein signaling machine. As signaling events are initiated within a minute of contact, the rapid increase in contact area and clustering of receptors during early spreading are critical features of the immune response. The dynamics of the membrane and cytoskeleton during contact formation and their effect on signaling is not well understood. We have studied the morphology of the membrane, dynamics of the actin cytoskeleton and simultaneously the spatiotemporal localization of signaling clusters during the very early stages of spreading. Formation of signaling clusters was closely correlated with the movement and topography of the membrane in contact with the activating surface. Further, we observed membrane waves driven by actin polymerization originating at these signaling clusters. Actin-coupled membrane waves likely play an important role in force generation at the immune synapse, which is a topic of current investigation. Membrane deformations induced by such wavelike organization of the cytoskeleton may be a general phenomenon that underlies cell-substrate interactions and cell movements.

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## Sensitivity Analysis of a Three-Species Non-Linear Response Omnivory Model

We investigate a three-species omnivory model with non-linear Holling Type II functional and numerical responses. Our coupled system of differential equations incorporates the definition of omnivory—feeding on more than one trophic level—using thirteen model parameters and three state variables. The state variables correspond to species densities for a top predator, an intermediate consumer and a basal resource. As estimates from natural systems, the model parameters are subject to natural intrinsic variability and measurement error. We use sensitivity analysis to determine how infinitesimal changes in parameters, corresponding to variability and error, affect the population densities. We apply theorems on continuous dependence and differentiability with respect to parameters to our model to derive sensitivity equations. After solving the sensitivity equations which are "forced" by the original coupled system we compare the sensitivities using a weighted norm. Our comparison shows that small changes in the top predator mortality rate cause the greatest change in the species densities. Thus, biologists should take extra care in the field to accurately collect data to determine the top predator mortality rate. Also, we determine the least sensitive parameter to be the top predator handling time of the intermediate consumer. Overall, the handling times are less sensitive with the search and mortality rates being the most sensitive.

# Modeling adhesion of *bacteria* to artificial surfaces under flowing conditions

Scott Van Epps

Bloodstream infections associated with intravascular devices are becoming the most frequent cause of community acquired bacteremia –approximately 500,000 central venous lines become infected in the United States annually. Most experimental and modeling work has focused on the behavior of established communities. However, the genesis of biofilms on bloodstream devices is essentially the tipping of a balance of forces upon a bacterium making an otherwise convective random flight past a susceptible artificial surface. Local hydrodynamic shear imposed by the carrier fluid must be overwhelmed by specific or non-specific attraction between a bacterium and a target surface in order for adhesion to proceed.

Not surprisingly, observations of this behavior are affected by the tremendous variety in choice of experimental conditions, including flow cell geometry, carrier fluid viscosity and ionic strength, surface composition, and bacterial species and growth conditions. As a result, it is difficult to compare experimental results from report to report.

Here, I discuss the relevant physics of the problem of bacterial adhesion under flowing conditions as well as summarize the experimental techniques available for quantifying the various mechanical and electrochemical forces felt to participate in bacteria-surface interaction. I then discuss some of the mathematical treatments that have been previously reported, with a specific eye towards their utility in evaluating experimental results in microfluidic adhesion experiments monitored with videomicroscopy.

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## A Mathematical Model of the Influence of Hydrodynamics on Quorum Sensing in Bacterial Biofilms

Quorum sensing is the process where bacteria monitor their population density through the release of extra-cellular signalling molecules. The presence of these molecules allows bacteria to coordinate gene expression throughout the population. This process has been studied primarily in planktonic batch cultures where it is characterized primarily by a critical population density at which a quorum is induced.

In nature, bacteria predominantly form biofilms where they have been shown to be physiologically distinct from free swimming bacteria of the same species. Unlike the signal levels in batch cultures, environmental signal levels could be affected by the hydrodynamic environment in several ways. Here, we focus on two main external processes affecting the signal concentration: the diffusion of signal produced within the biofilm into the bulk fluid and the mass transfer of the signal out of the local environment due to the presence of a fluid flow over the biofilm surface.

In this study, the communication within and between bacterial biofilm colonies is the primary concern. While the shape of the biofilm can vary due to many different conditions such as the type and availability of the substrate (carbon source) used to grow the biofilms, we consider two different biofilm shapes: biofilms that have formed into continuous sheets and circular biofilms, which are idealized biofilms with a circular cross-section. We model the interaction between the signal concentration and the hydrodynamic environment using a two-dimensional mathematical model for the production, diffusion, advection, and degradation of the signalling molecule coupled with a laminar fluid flow. This coupled fluid flow/transport equations are solved numerically using finite element methods.

The presence of the hydrodynamic environment has numerous effects on the quorum sensing process. First, the presence of the fluid flow suppresses the maximum signal concentration in the domain, increasing the critical biomass density for a quorum to be induced as the flow rate is increased. This observation is expected and has been confirmed experimentally. Second, the presence of non-uniformity in the biomass density in the domain has a strong effect on the onset of a quorum. The critical signal density can be reached if there is a sufficient biomass concentration in a small region and, coupled with the advection of the signal, this can cause a significant portion of the biofilm to reach a quorum even if the total biomass density is below the critical biomass density observed in a planktonic batch culture. This leads to the observation that the conditions under which the biofilm is developed, which influences the biomass distribution in the film, can influence the experimentally measured critical biomass for a quorum to be reached. Lastly, it is observed that the advection of the signal downstream facilitates communication between isolated colonies over a finite distance that varies with the flow rate, allowing colonies that do not possess sufficient biomass for a quorum to be reached in isolation to reach a quorum due to a signal from an upstream colony.

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## A computational biology approach predicts that NKT and MAIT invariant TCRα sequences can be produced efficiently by VJ gene recombination.

T cells express receptors on their surface that enable the recognition of pathogen peptides. These T cell receptors (TCRs) are comprised of two polypeptide chains, the α- and β-chains. A diverse repertoire of TCR α- and β-chains is produced in the thymus by recombination of an individual's original (i.e. germline) TCR genes. The germline genes involved in this process include the variable (V), diversity (D; for β-chain only), and joining (J) genes. The cleavage of nucleotides from, and the addition of nucleotides to, the end of the gene segments generates additional TCR diversity. The process of gene recombination can generate an enormous potential diversity of TCRs in the thymus (eg. $>10^{18}$ in humans), which greatly exceeds the number of T cells found in the peripheral T cell repertoire of an individual at any given time (eg. $\sim10^{12}$ in humans). The amino acid sequence across the V-(D)-J gene segment junction, referred to as the CDR3, is an important determinant of the TCR's ability to interact with a pathogen peptide.

Natural killer T (NKT) and mucosal-associated invariant T (MAIT) cells are specialized, highly effective subsets of T cells with various roles in immunity. Both NKT and MAIT cells typically express semi-invariant TCRs that are comprised of an invariant TCR α-chain. NKT and MAIT TCR α-chains use invariant V and J gene combinations and feature ubiquitous canonical CDR3α amino acid sequences across the VJ junction that are dominant in a majority of individuals and highly similar across species. The prevalence and evolutionary conservation of the NKT and MAIT TCRs suggest that they play an important role in the immune system and thus it is surprising that their production is left to chance by the largely random gene recombination process. In this study, we use a computational biology approach, involving bioinformatics analysis and computer simulations of the gene recombination process, to investigate whether the efficiency of the production of the NKT and MAIT TCR α-chains could explain their prevalence across individuals and species. We surveyed studies reporting NKT and MAIT TCRα sequences for a variety of species. For all reported species, the NKT and MAIT invariant TCRα amino acid sequences can be encoded by at least one germline-derived nucleotide sequence, requiring no random nucleotide additions. Moreover, an "overlap" between the Vα and Jα genes enables nucleotides from either of the Vα or Jα genes to contribute to the formation of codons at the VJ junction. Consequently, the invariant TCRα amino acid sequences can be produced by a large variety of recombination mechanisms through a process of convergent recombination. In computer simulations of a random recombination process involving the invariant NKT and MAIT TCRα gene combinations, the human and mouse NKT and MAIT invariant TCRα amino acid sequences were the most generated of all sequences conforming to the CDR3α length restrictions associated with NKT and MAIT cells. These results suggest that the highly efficient production of the NKT and MAIT invariant TCRα sequences is an important determinant of their prevalence within individuals, across individuals, and across species.

## Discrete Event Branching Process Model of Memory CD4+ Memory T cell differentiation

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Much work has been done looking at CD4+ Memory T cells, our research isolates the individual events that occur to CD4+ T cells throughout an immune response. Memory CD4+ T cells are the cells that orchestrate a response to a pathogen upon re-challenge, and the memory T cell repertoire is created during primary and subsequent infections or through vaccination. Understanding this generation can lead to better developments of vaccines and a greater understanding of immune responses to infections. We generate a Discrete Event Branching Process to represent the events that occur during the development of the CD4+ T cell lineage. We are looking to understand the probability distributions associated with each step that occurs over the course of development, and then determine the variation from traditional deterministic models. We then use Python to run simulations to track a CD4+ T cell throughout an immune response over a 400 hour interval, receiving constant antigenic stimulation. We track over each time step the number of naive CD4+ T cells, effector CD4+ T cells, Memory CD4+ T cells, and total CD4+ T cell count. We then perform a sensitivity analysis of estimated parameters to understand the influence they have on our system. Our simulation yields results to show the variation from deterministic curves of an immune response along with overlaying the curves determined by the mean of all trials and plus or minus one standard deviation, and we also calculate the mean number of mitoses a cell will have before undergoing apoptosis, which supports the observation of different responses to the same pathogen in different individuals, and can be used to understand the parameters that exist when considering treatments to pathogens such as vaccine development.

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## Quorum Sensing Interaction and the Effect of Antibiotic on the Dynamics of Two Types of Bacteria

Quorum sensing regulates bacterial population density through the production of signal molecules or to initiate biofilm formation, which increases resistance against antibiotics. When this process occurs, signal molecules are produced and released into the surroundings. Signal molecules induce some bacteria to produce even more signal molecules, a phenomenon known as autoinduction. Fast and slow growing strains of the same bacterial species were investigated, in which four ordinary differential equations were used to model the dynamics of these strains, antibiotic, and the signal molecule in the system. Only the fast-growing strain was capable of producing signal molecules. These molecules induce some of the fast-growing strain to convert to the slow-growing strain, which is more resistant to the antibiotic. Using numerical and analytical methods, equilibria and stability were analyzed with and without autoinduction. Three types of equilibrium can occur depending on parameter values. In one case, both of the bacterial strains were completely eliminated by the antibiotic, indicating a successful therapeutic treatment. In a second case, only the slow-growing strain survived, and in a third case both strains survived. Even though the first two cases can be stable, they may not be desirable since microbial organisms still exist, which can potentially lead to a chronic and persistent infection. When autoinduction was present, few differences were noted when compared to the data without autoinduction. However, autoinduction may still have effects on the dynamics when the antibiotic is dosed periodically or may have an impact on the duration of the infection.

**Dorothy Wallace,** Dartmouth College**,** Hanover, NH, USA

## Modeling predator-prey equations for *Ambystoma tigrinum* in the presence of phenotypic plasticity

Phenotypic plasticity is the ability of an organism to mature into a variety of phenotypes from a single genotype. *Ambystoma tigrinum,* the tiger salamander, is a classic example of this phenomenon. A species of salamander widespread in the U.S., the tiger salamander hatches from eggs into an aquatic larval form. In a ``typical'' growth trajectory, the larval form matures into an adult salamander capable of terrestrial life, then becomes sexually mature. Other trajectories include remaining in a legless aquatic form but maturing sexually to carry out the entire life cycle in the water or, in a variant of this, developing huge jaws in the juvenile stage and becoming an aquatic, largely cannibalistic predator. The model we construct has four trophic levels. Fairy shrimp and other minute organisms at the bottom of the food chain are eaten by recently hatched salamander larvae, or ``young of the year'' and also by an assortment of other predators of similar size. The young of the year mature into one of two possible forms, either a larger larva that is a sexually immature juvenile or a cannibalistic form of the juvenile. These in turn mature into three forms of adult capable of reproduction. We show that that the various populations of *Ambystoma tigrinum* are highly sensitive to small variations in the morphological choice, both in the full model and in a all submodels including more than one adult phenotype. The model is also shown to display limit cycles for some parameter choices.

This research was conducted with the assistance of 64 undergraduates in two sections of a course in differential equations.

Keywords:
Ecology, Ecosystems, Evolutionary biology

## Title: 2D Swimming at Low Reynolds Number

## Presenting author: Qixuan Wang

**Author affiliations**: School of Mathematics, University of Minnesota, MN, USA

## Abstract:

(This is an extension of the minisymposium 25: Multiscale modeling of cell movement, organized by Chuan Xue and Qixuan Wang.) Cell migration is crucial for many biological processes. To date, a lot have been done for cells crawling. We are interested in another mode of migration—self-propelled swimming at low Reynolds number, in which both inertia and the interaction between the cell and the extracellular matrix are absent. In such environment, the cell's migration relies only on appropriate sequencial shape changes of the cell body. By mathematically generating general shape deformations of planar Stokes flow swimmers, we study the interaction between the cell body and the surrounding fluid, discover those factors that play crucial roles in the swimming process and prescribe what kind of shape deformations may lead to more efficient swimming.

**Xueying Wang**, Texas A&M University, College Station, TX, USA
Raju Gautam, Pablo J. Pinedo, Renata Ivanek, Texas A&M University, College Station, TX, USA

## A stochastic model for transmission, extinction and outbreak of *Escherichia coli* O157:H7 in cattle as affected by ambient temperature and pathogen cleaning practices

Many important infectious agents transmit through contaminated environment where they may persist. Their persistence in the environment is determined by the temperature dependent rates of their growth (replication) and by cleaning (sanitation) modulated rates of their clearance from the environment. To elucidate the effect of these factors on the infection transmission dynamics, extinction and outbreak, while accounting for the random nature of the infection transmission process, this study proposes a stochastic-differential-equation model as an approximation to a Markov jump process model, using *Escherichia coli* O157:H7 in cattle as a model system. In the model, the within host population infection dynamics are described using the standard susceptible-infected-susceptible framework, and the *E. coli* O157:H7 population in the environment is represented by a compartment that measures the free-living pathogen size. In this work, the Kolmogorov backward equations that determine the probability distribution and the expectation of the first passage time were rigorously derived in general settings. As an application of the theoretical results to *E. coli* O157:H7 infection in cattle, the first infection extinction and outbreak were investigated by numerically evaluating the Kolmogorov equations that solve the associated probability density function of the process governed by the corresponding stochastic model and the associated mean of the corresponding stopping time. The results provided an insight into *E. coli* O157:H7 transmission, and suggested ways of controlling the spread of infection in a cattle herd. Specifically, the study indicates importance of ambient temperature and cleaning during summer season.

# The role of glucose-dependent mobilization and priming of insulin granules in the biphasic insulin secretion

I. Johanna Stamper[1,2], **Xujing Wang**[1,2]

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Insulin is the primary regulating hormone of blood glucose, and is produced and release by the pancreatic islet beta cells. A normal beta cell contains an excessive amount of insulin granules, and only a small proportion is ever used. This is even true even under pathological conditions such as diabetes, where demand for insulin is increased but not adequately compensated. The rate limiting steps in insulin secretion, and why the diabetics cannot tap into the vast insulin reserve inside beta cells, are not well understood.

In this study we develop and analyze a mathematical model of glucose-induced insulin secretion from pancreatic islet beta-cells. We assume that insulin granules reside in different pools; also, consistent with recent experimental observations, our model accounts for the fusion of newcomer granules that are not pre-docked at the plasma membrane. In response to a single step increase in glucose concentration, our model reproduces the characteristic biphasic insulin release observed in multiple experimental systems, including perfused pancreata and isolated islets of rodent or human origin.

From our model analysis we note that first-phase insulin secretion depends on rapid depletion of the primed, release-ready granule pools, while the second phase relies on granule mobilization from the reserve. Moreover, newcomers have the potential to contribute significantly to the second-phase. When the glucose protocol consists of multiple changes in sequence (a so-called glucose staircase), our model predicts insulin spikes of increasing height as seen experimentally. In contrast to previous mathematical models, in which the staircase experiment was reproduced by assuming heterogeneous beta-cell activation, we assume a fully homogeneous beta-cells population. In our model the increasing spikes in insulin secretion instead stem from the glucose-dependent increase in the fusion rate of insulin granules at the plasma membrane of single beta-cells. In light of experimental data indicating limited heterogeneous activation when beta-cells are arranged within islets, our findings suggest that a graded, dose-dependent cell response to glucose may contribute to insulin secretion patterns observed in multiple experiments, and thus regulate *in vivo* insulin release.

**John Ward**, Loughborough University, UK

## Modelling of cold plasma treatment of biolfilms

Biofilms are slimy colonies of bacteria growing on solid-fluid interfaces. Their natural resistance to anti-microbial agents causes considerable concern in medicine and industry. Cold plasma jets has been used for some years as a means of sterilising surfaces against bacterial biofilms and more recently this approach has been considered for use in medicine. The cold plasma jet itself does not penetrate very deep into the biofilms, but the byproducts that the jet creates do, and these do most of the damage.
In this talk we discuss a hybrid continuum/individual-based modelling framework designed to simulate biofilm growth in 2/3-dimensions, and describe how it can be extended to simulate the action of the plasma byproducts. Simulations will be presented investigating the effect of treatment in two experimental setups and at various stages of biofilm maturity. Key results from this analysis will be discussed.

Talitha M. Washington, Howard University, Washington, DC, USA

## Designing a Research-Based Mathematical Biology Course

Mathematical biology is an emerging field which has caught the interest of many undergraduates and graduate students alike. Unfortunately, it is not clear how to best prepare our students for career in the mathematical biosciences. In this talk, we discuss best practices from designing a mathematical biology course at Howard University based on current research articles in the field.

Keywords. Education and Systems biology.

**Variational multiscale models for ion channel transport**

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A major feature of biological sciences in the 21st Century will be their transition from phenomenological and descriptive disciplines to quantitative and predictive ones. Revolutionary opportunities have emerged for mathematically driven advances in biological research. However, the emergence of complexity in self-organizing biological systems poses fabulous challenges to their quantitative description because of the excessively high dimensionality. A crucial question is how to reduce the number of degrees of freedom, while preserving the fundamental physics in complex biological systems. This work focuses on a new variational multiscale paradigm for biomolecular systems. Under the physiological condition, most biological processes, such as protein folding, ion channel transport and signal transduction, occur in water, which consists of 65-90 percent of human cell mass. Therefore, it is desirable to describe membrane protein by discrete atomic and/or quantum mechanical variables; while treating the aqueous environment as a dielectric or hydrodynamic continuum. I will discuss the use of differential geometry for coupling microscopic and macroscopic scales on an equal footing. Based on the variational principle, we derive the coupled Poisson-Boltzmann, Nernst-Planck (or Kohn-Sham), Laplace-Beltrami and Navier-Stokes equations for the structure, dynamics and transport of ion-channel systems. As a consistency check, our models reproduce appropriate solvation models at equilibrium. Moreover, our model predictions are intensively validated by experimental data. Mathematical challenges include the well-posedness and numerical analysis of coupled partial differential equations (PDEs) under physical and biological constraints, lack of maximum-minimum principle, effectiveness of the multiscale approximation, and the modeling of more complex biomolecular phenomena.

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**Nathan Weinstein** and Luis Mendoza, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Distrito Federal, México.

## A Computational Model of the Network that Controls Fate Determination and Cell Fusion in the Vulval Precursor Cells of *Caenorhabditis elegans*

The vulva of *Caenorhabditis elegans* has been used as a model for the study of cell differentiation and organogenesis for more than three decades. In this system the signaling cascades of WNT, Ras/MAPK and NOTCH interact with each other forming a molecular network, but the precise topology and dynamics of this network is incomplete. By making an exhaustive search of the experimental literature, we built a multivalued, discrete, synchronous model of the molecular network that controls cell fusion and fate determination in the vulval precursor cells of *Caenorhabditis elegans*. The proposed model is the first to include the Hox genes *lin-39, mab-5* and *ceh-13*, the WNT signaling pathway with the polarity defining genes, most of the components of the Ras/MAPK and NOTCH signaling pathways, the fusogen *eff-1*, and the genes that regulate its transcription. After simulating the dynamic behavior of the model we found steady patterns of gene expression and protein activity that correspond to those reported in the literature for each cell type; vulval precursor, first fate, second fate, second fate with reversed polarity, third fate and fusion fate. Moreover, we were able to simulate the fusion of cells, the determination of the first fate, second fate, the transition from the second fate to the first fate and the determination of the third fate under the right environmental conditions. Finally, the model was used to simulate all possible single gene loss- and gain-of-function mutants, as well as some double and triple mutants. We were able to associate most of these simulated mutants to multivulva (Muv), vulvaless (Vul), egg-laying defective (Egl), or defective polarity (Biv) phenotypes.

**Joshua S. Weitz,** School of Biology & School of Physics, Georgia Institute of Technology, Atlanta, GA, USA
Bart Haegeman, INRIA Research Team MERE, UMR MISTEA, Montpellier, France

## A Neutral Theory of Genome Evolution and the Frequency Distribution of Genes

The gene content of genomes of closely related bacteria can differ significantly. For example, pair-wise comparisons of genome sequences from isolates of the same species often do not share a substantial fraction of their gene content. When a large number of genomes within a bacterial "species" are sequenced, the gene content variability can be summarized as a gene frequency distribution: given *G* sequenced genomes, some genes are found in *k* of these genomes where *k* ranges from 1 to *G*. Empirically, such gene frequency distributions possess a characteristic U-shape, such that there are many genes that only appear in one genome, fewer genes which appear in an intermediate number of genomes, and many genes which appear in all genomes. Genes within each of these three categories have been labeled accessory, character and core genes, respectively[1]. It would seem that U-shaped gene frequency distributions can be used to infer the essentiality and/or importance of a gene to a species. Instead, we ask: is it possible to recapitulate findings of U-shaped gene frequency distributions in the absence of selective forces driving genomic and population composition?

Here, we answer this question in the affirmative by proposing a simple and analytically tractable neutral model of genome evolution that explicitly accounts for gene composition of genomes. In this model, genomes undergo birth-death processes in a neutral sense and also acquire and lose genes. The model differs from most previous efforts to analyze genome evolution by self-consistently treating the dynamics at two scales: population level drift and genomic level change. We analyze our model using coalescent theory and derive closed form solutions for gene frequency distributions. We find that gene frequency distributions in the model possess a characteristic U-shape even in the absence of selective forces driving genome and population structure. We fit model predictions to empirical data from 6 bacterial pathogens: *B. anthracis*, *E. coli*, *Staph. aureus*, *Strep. pneumoniae*, *Strep. pyogenes* and *N. meningitides*, using a bioinformatics pipeline for assessing gene-genome composition[2]. In so doing, we find a reasonable correspondence between our neutral model and data from six distinct bacterial species with sequenced genomes from multiple isolates. However, our model assuming constant population sizes predicts gene frequency distributions with systematically fewer rare genes than the empirical distributions.

Hence, we also consider variations to our base model. These variations include cases of constant and exponentially growing population sizes as well as two alternative models which contain a "rigid" and "flexible" core component of genomes. All of these models can improve fits to empirical distributions. In addition, all of these models make a number of other predictions regarding the scaling of sample core and pan genome sizes in accord with observations. Together, these models suggest that U-shaped gene frequency distributions provide less information than previously suggested regarding gene essentiality. Hence, we discuss the need to find patterns of genome composition variation other than gene frequency distributions that can be explained by neutral models and identify those patterns or deviations from patterns that cannot be explained by neutral models. In addition, we briefly highlight the need for additional theory to disentangle the roles of evolutionary mechanisms operating within and amongst individuals in driving the dynamics of gene distributions.

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**Chad Wells**, University of Guelph, Guelph, Ontario, Canada
Chris Bauch, University of Guelph, Guelph, Ontario, Canada

## The Impact of Personal Experiences with Infection and Vaccination on Behaviour-Incidence Dynamics of Seasonal Influenza

Background: Personal experiences regarding past vaccination and infection events are strong predictors of future vaccine acceptance. Mathematical models can be used to capture the feedback between personal vaccine choices as influenced by personal history, and disease dynamics.

Objectives: To evaluate 1) the impact of past personal events on vaccine coverage; 2) what factors are most influential in the stability of vaccine coverage; and 3) whether vaccine opinions can become correlated in a perfectly rational network.

Methods: We coupled disease dynamics with individual vaccination decisions where personal influenza and vaccination experiences are included in the decision making process. In addition to influenza, we incorporated influenza-like-illness (ILI) into the decision-making, where a percentage of the population will mistake ILI for influenza. An individual's choice to vaccinate is influenced by their most recent experience with infection, vaccine complications and perceived vaccine efficacy. Our stochastic network model allows for further investigation into issues such as correlation of vaccine opinions on networks and factors that lead to variation in vaccination coverage from season to season. Infection is transmitted from an infectious node to a neighbouring susceptible node with some probability per day.

Results: We found that when individuals are able to recall past events for a longer period of time there, vaccine coverage becomes significantly more stable. We also noticed that as we lengthened memory, vaccine coverage increased, even though past vaccine complications would be recalled for longer as well. However, we identified a threshold where vaccination coverage started to decline after lengthening memory further. We also found that more slowly waning vaccine immunity stabilises vaccine coverage; however, there was also a decrease in coverage. The nature of close contact infection on the network, coupled with the history dependent decision-making, resulted in positively correlated vaccination strategies between neighbours, despite the absence of imitation in the model.

Conclusions: Flu vaccines conferring long-term immunity are currently in development. Our model suggests that behavioural feedbacks should be considered when developing such "universal" flu vaccines, since these can cause sporadic and unpredictable outbreaks for some of our parameter choices. Our results suggest that public health messaging should focus on reminding individuals about past infections in order to increase overall vaccine coverage and prevent unexpected drops in coverage, while at the same time reassuring the public about vaccine efficacy.

**Marleen Werkman**[1], Ellen Brooks-Pollock[2], Matt J. Keeling[1] and Michael J. Tildesley[1]

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**Investigating the effectiveness of regionalized movement bans for the control of foot and mouth disease in the UK**

Foot and mouth disease (FMD) is a highly infectious disease that primarily affects cloven-hoofed animals (such as cattle, sheep and pigs) and typically causes fever and blisters in the mouth and on the feet resulting in lameness. Whilst death of livestock is rare, outbreaks of FMD in previously disease-free regions can have huge economic repercussions and devastation to the farming industry, owing to the introduction of movement restrictions, export bans and culling of livestock.

In the United Kingdom there have been two relatively recent outbreaks of FMD. In 2001 a large nationwide epidemic occurred; over 2000 farms were infected and a further 8000 had their livestock culled in an effort to control the disease. The costs of this epidemic have been estimated around £8 billion pounds. In 2007, a small outbreak occurred in Surrey in the South East of England. This outbreak was rapidly contained with only eight farms being found positive throughout the epidemic.

FMD can be transmitted between farms at a local level by direct contact between susceptible and infected livestock, via aerosol spread and via fomites (i.e. contaminated vehicles or farm equipment). However, live animal movements can result in the disease being disseminated over a large geographical area. In the UK, cattle require an ear tag with a unique number; this is to ensure that all animals have a unique identity and that births, deaths and movements on and off farms can be registered for each animal. Records are registered through the Cattle Tracing System, which is run by the British Cattle Movement Service (part of the Department for Environment, Food and Rural Affairs, DEFRA).

Current UK policy in the event of a future FMD outbreak is to introduce a nationwide movement ban as soon as possible after the first reported case. However, a policy in which movement control is introduced at a regional level may minimize the economic impact of the disease, reduce the inconvenience to farmers and still prevent a large epidemic.

We present a metapopulation model that includes local and movement-based spread to test alternate movement ban policies and their effectiveness in reducing spread of disease. We investigate the effectiveness of banning movements (a) based upon proximity to previously reported outbreaks, (b) in regions of high livestock density and (c) in regions with high movement activity. These strategies are tested against the nationwide movement ban policy introduced in 2001 to investigate whether livestock movements could be permitted within certain regions during future outbreaks. The results of this study could be used to modify nationwide movement ban policies and reduce the economic impact of future outbreaks of disease in the livestock industry.

## Resistance development to molecular targeted treatment strategies

**Benjamin Werner**
Research Group for Evolutionary Theory, Max-Planck-Institute for Evolutionary Biology, Plön, Germany

Abstract: Most cancers are caused by either a single mutation, or more often, an accumulation of mutations and thereby altered cell differentiation properties. Nowadays, many of these mutations are known and in individual cases, as for example Chronic Myeloid Leukemia, molecular targeted drugs were developed. These drugs successfully changed clinical treatment protocols and converted ultimate life-threatening diseases into chronic diseases. Unfortunately, cancer cells tend to develop resistance, leading to treatment failures. This is an increasing problem for clinical treatment routines. Thus, detecting and understanding the effects of these mutations early is crucial. Here, we analyze a resistance inducing experiment by applying a minimalistic mathematical model. From this, one can obtain the dynamical patterns of the population on its way to resistance as well as important system parameters, highlighting different resistance mechanisms.

**Diana White**, University of Alberta, Edmonton, AB, Canada

## A mathematical model for pattern formation of microtubules in the presence of motor proteins

Microtubules, rigid protein polymers found in cells, can be organized into various patterns under the influence of motor proteins. Such patterns are crucial for normal cellular function and development. In this talk, I introduce an integro-differential equation model that describes how microtubules reorganize in space and time, in the presence of motor proteins, to form various patterns in two-dimensional space.

I first discuss the development of the model that is based on three key assumptions. In particular, our model describes how microtubules evolve in space and time under the assumptions that 1) microtubules can treadmill (they can shrink from one end at the same rate that they grow from the opposite end), 2) they can grow and shrink from their positive end, and 3) they can reorient themselves by interacting with motor proteins.

After describing the development of the model, I will present preliminary numerical and analytical results that describe how microtubule distributions evolve in time in two space dimensions. By exploring different regions of the model's parameter space we observe different patterns for the microtubules. In particular, microtubules interacting with high densities of motors tend to form bundled organizations (parallel arrays), while microtubules interacting with low densities of motors tend to form astral organizations (radial arrays).

**K A Jane White**, Centre for Mathematical Biology, University of Bath, UK

Vicki Brown, Ecology and Evolutionary Biology, University of Michigan

**Understanding the impact of vaccination strategy: HPV as a case study**

Vaccination against the human papillomavirus (HPV) is a recent development in the UK, implemented as part of a prophylactic treatment regime to reduce incidence of cervical cancer – HPV is detectable in more than 99% of cervical cancer cases.

Whilst HPV is an infection for which there is no long-lasting induced immunity post-infection, a single exposure to the virus is sufficient to initiate the cascade of events which eventually lead to cervical cancer. HPV is thought to infect around 80% of the sexually active female population at some point during their lives. Of these, 10-20% have a persistent infection, lasting more than 6 months; such infections increase the likelihood of developing precancerous lesions which may then develop further into cancer. To date, whilst the male population is also susceptible to HPV infections, no links have been made between these infections and male cancers. Transmission of the virus takes place as a result of intimate contact, such as results from sexual interactions, between an infected and susceptible individual. Therefore we consider HPV as a sexually transmitted infection.

In order to benefit from the protection afforded by the HPV vaccine, individuals must be vaccinated prior to exposure to HPV. In the UK this is achieved by developing a vaccination strategy aimed at girls aged 12-13 and implemented through a school vaccination programme. This age choice means that the majority of individuals have not been exposed to HPV; moreover, given that the vaccination efficacy may wane over time, it provides the 'maximum' length of protection once exposure to HPV occurs (the rate of onset of sexual activity is greatest for young people aged 15-17 years in the UK). Currently the vaccination is thought to have an efficacy in excess of 6 years. Additional, 'catch-up' vaccination is also being used for girls aged around 17 years in the initial phase of the programme.

We use mathematical modelling, based on a compartmental model to describe the infection dynamics and extended to explore optimal control scenarios, to address the following questions:

- How does a vaccination programme with a fixed target coverage impact the prevalence of infection?
- How does waning immunity and time to sexual debut following vaccination impact the efficacy of the vaccination programme?
- What is the optimal vaccination strategy if cost of infection must be balanced by cost of vaccination programme?
- What impact would male vaccination have on the predictions from a female only vaccination programme?

**Kathleen Wilkie**, Center of Cancer Systems Biology, Tufts University School of Medicine, Boston, MA, USA
Philip Hahnfeldt, Center of Cancer Systems Biology, Tufts University School of Medicine, Boston, MA, USA

## Immune Modulation of Tumor Growth Through Inflammation and Predation

Cancer cells can elicit an immune response in the host, which is generally tumor-suppressive, but for weak responses may actually be tumor-promoting. We propose that this complex dynamic may be understood as a process of immune stimulation by the tumor, followed by cytotoxic targeting by the immune cells, which acts to alter tumor size and growth characteristics and subsequent immune stimulation. Just how these influences interact has complex implications for tumor development and cancer dormancy.

To show this, we have developed a two-compartment model consisting of a population of cancer cells and a population of immune cells. The model incorporates the combined effects of the various immune cell types, exploiting general principles of self-limited logistic growth and the physical process of inflammation, which, as will be discussed, may be either tumor-promoting or tumor-inhibiting.

A Markov chain Monte Carlo method is used to determine parameter sets that predict tumor growth equally well, but at the same time also predict fundamentally different underlying dynamics. The results underscore the ultimately polar nature of final tumor fate (escape or elimination), while at the same time showing how persistent regions of near-dormancy may precede either of these two outcomes.

Another important finding is that near- and long-term responses of a tumor to immune interaction may be opposed; that is to say, a response dynamic that appears to be more promoting of tumor growth than another in the near term may be superior at curtailing tumor growth in the long-term, even to the point of establishing dormancy while the other allows for tumor escape.

The striking variability observed even in this simple model demonstrates the significance of intrinsic and unmeasurable factors determining the complex biological processes involved in tumor growth in an immune competent host. Consequences and biological interpretations of this work will be discussed in terms of treatment approaches that exploit immune response to improve tumor suppression, including the potential attainment of an immune-induced dormant state.

**Ovarian tumor attachment, invasion and vascularization reflect unique microenvironments in the peritoneum: Insights from *intravital* imaging and mathematical modeling**

Kimberly Kanigal-Winner[2,] Mara P. Steinkamp[1], Melanie Moses[4], Carolyn Muller[3], Robert Hoffman[5], Yi Jiang[6] and **Bridget S. Wilson[1]**

Departments of [1]Pathology, [2]Biology, [3]OB/GYN and [4]Computer Science, University of New Mexico, Albuquerque, NM 87131; [5]AntiCancer Inc, San Diego, CA; [6]Department of Mathematics, Georgia State University, Atlanta GA 30302

We have established a xenograft model of human ovarian cancer relapse using SKOV3ip cells stably expressing GFP or RFP. Tumor cells are engrafted in nude mice by intraperitoneal injection, followed by intravital imaging of tumor attachment, growth and invasion after 1, 2 and 3 weeks. We report remarkably different tumor growth characteristics at distinct attachment sites, including spleen, omentum, and stomach/intestine, despite the similarities in the mesothelial lining on each surface. Once past the mesothelium, tumors attached to the spleen or omentum readily invade the "open" architecture of spleen and omentum. In contrast, tumors attached to the stomach or intestine are poorly invasive; rapid tumor expansion into the peritoneal space is supported by new blood vessels that extend from the outer lining of the stomach and intestine. Simulations of these complex processes are based upon the Cellular Potts computational framework. Modeling parameters, including the biomechanical constraints of tissue, relative adhesion between all cell types, chemotactic gradients and angiogenesis are derived from experiments. By combining experimental and simulation approaches, we gain important insights regarding the influence of the microenvironment on tumor growth, morphology and neo-vascularization.

**Jeremy Wojdak**, Radford University, Radford, VA, USA
Joel Hagen, Radford University, Radford, VA, USA
Fred Singer, Radford University, Radford, VA, USA
Jill Stewart, Radford University, Radford, VA, USA
Juergen Gerlach, Radford University, Radford, VA, USA

**SUMS4BIO – Increasing quantitative sophistication across the undergraduate biology curriculum: horizontal and vertical integration across courses.**

Faculty in the Departments of Biology and Mathematics and Statistics at Radford University will cooperate in developing strategies and materials for improving the quantitative skills of biology students. This project targets students entering the major with at- or below-average SAT math scores (mean RU Math SAT score = 511, national average = 515) and mathematical deficiencies identified by the ALEKS assessment instrument. Twenty-eight percent of these students are first generation college students, 16 percent are minorities, and 23 percent receive Pell Grants. To meet the needs of this student population, faculty teams will develop two new courses: a freshman level Mathematics for Biology course and a sophomore level Statistics for Biology course. The two departments will closely link the Mathematics for Biology course with two introductory biology courses: Ecology & Adaptation and Introductory Seminar in Biology. Because these linked courses will involve eleven contact hours per week, students will learn and practice fundamental quantitative skills at a pace that will not be overwhelming, but will encourage breadth and depth of exposure. Teams of faculty will design interdisciplinary course modules to engage students in activities that place fundamental quantitative skills in biological context through lab and field experiments closely linked to topics covered in lecture and discussion. The two departments will explicitly link the new Statistics for Biology course to Organismal Biology taken during the second semester of the sophomore year. Through an intentional plan of vertical integration, students will later expand and further develop these basic skills in the remaining three courses of the biology core curriculum and in most elective courses. Students interested in professional careers in biology will use this foundation as a stepping-stone to calculus and other higher-level mathematics courses. Here we meet students at a relatively low level of skill development and then incrementally develop their quantitative skills to more sophisticated levels.

## Evolving cross-talk in the neutrophil polarity network

**Lani Wu**
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How complex signaling networks shape highly-coordinated, multistep cellular responses is poorly understood. Here, we made use of a network-perturbation approach to investigate causal influences, or "cross-talk," among signaling modules involved in the cytoskeletal response of neutrophils to chemoattractant. We quantified the intensity and polarity of cytoskeletal marker proteins over time to characterize stereotyped cellular responses. Analyzing the effects of network disruptions revealed that not only does cross-talk evolve rapidly during polarization but also intensity and polarity responses are influenced by different patterns of cross-talk. Interestingly, persistent cross-talk is arranged in a surprisingly simple circuit: a linear cascade from front to back to microtubules influences intensities, and a feed-forward network in the reverse direction influences polarity. Our approach provided a rational strategy for decomposing a complex, dynamically evolving, signaling system and revealed evolving paths of causal influence that shape the neutrophil polarization response.

**Jason Harville, Stephanie Wu**, Kim Brown, Elise Hinman, Jonathan Klein, Nicholas Knoblauch, Helen Lam, Daniela Palmer, Kelsey Tanner, University of California, Davis, CA, USA

## Bugs, babies, and breast milk: a mathematical model

Human milk oligosaccharides (HMOs) are the third most abundant constituent of human breast milk after lactose and lipids, and yet they cannot be digested by infants. A common explanation for the abundance of HMOs is that they preferentially nourish beneficial bacteria, including members of the genus *Bifidobacterium*, in the infant's gut. These bacteria may subsequently grow faster and have a competitive advantage over other, possibly pathogenic, members of the infant gut microflora. Higher abundances of bifidobacteria are associated with health benefits such as disease resistance and vitamin production. Understanding the relationships between HMOs and human gut microflora may lead to advances in neonatal and infant medicine and aid in development of commercial products such as probiotics or infant formula.

A combination of ethical and practical considerations creates challenges in studying HMO metabolism. Direct sampling of gut microflora requires invasive procedures that would be unethical to perform on infants. Additionally, it is difficult to culture many species of gut microflora *in vitro*. For these reasons, researchers currently rely on genetic analysis of stool samples to measure the presence and abundance of microbes in the gut. Unfortunately, these analyses cannot resolve questions about mechanisms. In these situations, insight from mathematical models can help guide empirical work. Thus, the 2011 cohort of trainees in the UC Davis Collaborative Learning at the Interface of Mathematics and Biology (CLIMB) program (supported by the NSF-sponsored UBM program) developed a model of HMO metabolism by the human infant colon bacterial community to investigate the effects of HMOs on the relative abundances of key taxa.

The model consists of 23 differential equations that describe the dynamics of nine microbial taxa and 14 HMOs and HMO constituents. These equations incorporate rates of infux into and efflux out of the gut, microbial interaction with the 14 substrates, bacterial growth from feeding, and crossfeeding, a process in which HMOs are extracellularly degraded by certain microbial taxa with the resulting byproducts available to other taxa. We parameterized the model using time series data of single taxon metabolism of HMOs *in vitro*, and used it to predict the relative abundances of bacterial taxa in a multi-species environment. In order to simulate the natural differences in HMO composition among mothers, we ran our model using different subsets of HMOs. We also tested the effects of preferential feeding on community dynamics by incorporating instances of HMO preference among bacteria.

By simulating the process of HMO metabolism, we successfully predicted the relative abundances of key taxa found in some empirical studies. However, the model does not accurately describe some finer scale dynamics that occur on the order of days instead of weeks. In simulations, differing HMO compositions among mothers and preferential feeding behavior in bacteria each altered the order of relative abundances, indicating that these factors play a large role in community composition. Our predictions can be directly compared to empirical time series data, and the model itself provides a framework for future models. Such models should incorporate other potentially important factors, such as pH of the gut and interspecific competition among members of the gut microflora, in order to test the importance of these factors in determining community dynamics. It is our hope that future models based on this framework will be able to more accurately describe dynamics on the order of hours and days and predict the effects of short term therapies such as antibiotic or probiotic usage.

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## Coupling between switching regulation and torque generation in bacterial flagellar motor

The bacterial flagellar motor plays a crucial role in both bacterial locomotion and chemotaxis. Recent experiments reveal that the switching dynamics of the motor depend on the rotation speed of the motor, and thus the motor torque, non-monotonically. Here we present a unified mathematical model which treats motor torque generation based on experimental torque-speed curves and the torque-dependent switching based on the conformational spread model. The model successfully reproduces the observed switching rate as a function of the rotation speed, and provides a generic physical explanation independent of most details. A stator affects the switching dynamics through two mechanisms: accelerating the conformational flipping rate of individual rotor-switching units, which contributes most when the stator works at a high torque and thus a low speed; and influencing a larger number of rotor-switching units within unit time, whose contribution is the greatest when the motor rotates at a high speed. Consequently, the switching rate shows a maximum at intermediate speed, where the above two mechanisms find an optimal output. The load-switching relation may serve as a mechanism for sensing the physical environment, similar to the chemotaxis mechanism for sensing the chemical environment. It may also coordinate the switch dynamics of motors within the same cell.

# Multiscale Model of Platelet Aggregation

**Zhiliang Xu**
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Abstract: A multiscale computational model of thrombus (blood clot) development will be described which incorporates a submodel describing formation of fibrin network through fibrin elements representing regions occupied by polymerized fibrin. Simulations demonstrate that fibrin accumulates on the surface of the thrombus and that fibrin network limits growth by reducing thrombin concentrations on the thrombus surface and decreasing adhesivity of resting platelets in blood near thrombus surface. These results suggest that fibrin accumulation may not only increase the structural integrity of the thrombus but also considerably contribute toward limiting its growth.

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**Modeling the Effect of Diversity in Host Plant-Herbivore-Predator Interactions**

Predator and plant diversity can control Potato leafhopper (PLH) pest damage to the host-plant Alfalfa. New models of systems of differential equations were constructed using age structures, Allee effect, the Shannon diversity Index and other modeling approaches. Recent data and results on enemies and diversity hypotheses in field experiments were used to determine parameter ranges and validate the models. Parameters were adjusted to predict outcomes for scenarios not covered by field experiments and to examine their roles. This work provides a frame work for designing cost-effective and environmentally safe strategies to minimize alfalfa damage, and utilize enemies hypothesis and polyculture diversity.

**Atsushi Yamauchi**, Center for Ecological Research, Kyoto University, Otsu, Japan

## Optimal reaction norm for varying environmental states

It is sometimes observed that organisms alter their own phenotype in response to environmental variation without changing their own genotypes. This is called "phenotypic plasticity". This is referred to as "adaptive phenotypic plasticity" especially when the phenotypic change is an advantageous response. The plasticity can be represented as a series of phenotypic values on an axis of environmental states of which functional form is called the "reaction norm". If the reaction norm is a set of phenotypes optimized for each environmental state, its evolution is not significant from a theoretical viewpoint. In such a case, the reaction norm is an assembly of optimal solutions for the given environmental state which can be understood by a simple optimization approach.

However, evolution of the reaction norm is probably restricted by some factors. One possible constraint is a pleitoropy. When an organism changes its phenotype for one environmental state it may necessarily influence phenotypes for other states to some degree due to restrictions in gene expression or developmental processes. Another possible constraint is the cost of achieving the plasticity of phenotype. The organism may have to invest some cost to achieve mechanisms for plasticity, to develop the sensory system for environmental cue and the formation process of alternative phenotypes. Accordingly, an analysis of reaction norm evolution requires a different approach from simple optimization. Indeed, reaction norm evolution has been theoretically analyzed by some approaches that considered those constraints, *i.e.*, optimization, quantitative genetic model and gametic model (Scheiner, 1993).

I analyzed the optimal reaction norm from the viewpoint of optimization. In the model, an individual phenotype is divided into two components as $v_0+u(x)$. In this formulation, $v_0$ is a basal phenotypic level independent of environmental state, whereas $u(x)$ is an additional response to a given discrete environmental state $x$. Under the given environment state $x$, the phenotype $v_0+u(x)$ is considered to result in a success $f(x, v_0+u(x))$, accompanied by the total cost $c = k_1 v_0 + k_2 \sum_{x=1}^{X} u(x)^2$. The optimal reaction norm is obtained by maximizing $\Phi=f(x, v_0+u(x))-c$ with respect to $v_0$ and $u(x)$. Based on this approach, it is possible to discuss the general properties of the optimal reaction norm. Phenotypic plasticity may be intuitively expected to be advantageous under a significantly variable environment. However, I found that phenotypic plasticity may become less likely when environmental variations is large.

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Vitaly V. Ganusov, Department of Mathematics, Department of Microbiology, University of Tennessee, Knoxville, TN, USA

## Kinetics of CD8$^+$ T Cell Responses during Primary HIV-1 Infection

Despite numerous studies involving mathematical modeling of CD8$^+$ T cell responses to HIV, we lack understanding of basic principles in T cell immunology: how T cell responses to different epitopes of HIV are generated; how many responses there are; what role of the viral load in T cell kinetics is and whether T cells specific to different viral epitopes compete during the infection. Using recently published data from a cohort of HIV-infected patients that were followed from the onset of symptoms into the chronic phase, we address some of these questions. On average in a given patient there is 10 CD8$^+$ T cell responses specific to different viral epitopes. Surprisingly, the number of HIV-specific CD8$^+$ T cell responses (breadth of the response) changes very little from the earliest measurement to the chronic phase suggesting that most if not all T cell responses are generated in primary infection. Using a simple mathematical model for the kinetics of CD8$^+$ T cell response, we find that majority of epitope-specific CD8$^+$ T cells expand at the rate less than 0.1 day$^{-1}$ or double in size in more than 7 days (60%, median is 0.07 day$^{-1}$) and most of acute responses peak before 100 days post symptoms. There is a strong positive correlation between the estimated precursor frequency and maximum value of epitope-specific CD8$^+$ T cells reached during infection, and a strong negative correlation between the precursor frequency and the rate of expansion of epitope-specific T cells; the latter suggests intra-clonal competition between epitope-specific T cells. Finally, we find that although many CD8$^+$ T cell populations expand and contract in unison, in many cases (around 18%) there is evidence of competition between T cell responses such as change in magnitude of one response leads to a decrease in another response. These results provide basic immunological details on the kinetics of CD8$^+$ T cell responses to HIV, and also provide evidence that some but not all HIV-specific T cell responses compete during the infection.

**Guangming Yao**, Department of Mathematics, Clarkson University, Potsdam, NY, USA

## Meshless Solutions to PDE Model for Calcium Signaling in Ventricular Myocytes

Calcium dynamics plays a central role in studying the excitation-contraction (EC) coupling process which allows cardiac muscle cells to pump blood through the heart and around the body. For many reasons such as patient safety, mathematical models of calcium dynamics are becoming an increasingly powerful tool in the study of the heart and cardiomyopathy. Computational simulations can be used to model calcium movements in heart muscle cells and therefore simulate heart conditions.

In this paper, we model such calcium movements by a system of nonlinear diffusion-reaction partial differential equations (PDEs). Radial basis functions are used to provide a 'mesh-free' method for data reconstruction, as well as numerical solutions of the proposed PDE model. Two meshless methods are involved: the local radial basis function collocation method, and the localized method of particular solution methods. Two numerical methods discretize the time space in the differential model in an explicit and implicit way, respectively. The differences in terms of time step size and rate of convergence of the methods are compared. The numerical experiments show that predictions of calcium signaling process in ventricular myocytes with realistic transverse-axial tubular geometry and inhibited sarcoplasmic reticulum are extremely sensitive to the numerical methods used in the PDE model.

Computational simulations predict the calcium flows through the heart cells, which describe the excitation-contraction of the muscle. In particular, we compared the accuracy and efficiency of the computational methods in a realistic heart muscle cell. Due to the complexity of the cell geometry, currently it still takes an hour to model a single cycle of the EC process with only a small portion of the whole cell. However, the further assessment and improvement in the computational technique for solving the PDE model will enable more complex and detailed investigations of heart muscle disease.

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Ching-Shan Chou, Department of Mathematics, Ohio St, Columbus, OH, USA
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**Systems Biology of G-protein Sensing and Response during Cell Polarity**

A basic property of cells is polarity; from this asymmetry complex structures and behaviors arise. Cell polarity can be directed from internal or external cues. A common type of external cue is a chemical signal; the cell senses a gradient of the chemical, reorganizes its internal components (polarization), and then moves (chemotaxis) or projects (chemotropism) toward the source. This process occurs through receptor-mediated signal transduction pathways, and many of the best-studied examples involve heterotrimeric G-protein and small G-protein (Cdc42) systems.

There are many challenges associated with this complex behavior. In particular the cell must amplify a shallow external gradient into a steep internal gradient of components that are tightly localized in an all-or-none fashion. In addition, the cell must track the direction of the gradient which may be shifting. These performance objectives can be conflicting leading to a tradeoff. Another important challenge is filtering the input noise in the gradient.

In this talk, I will describe our analysis of mathematical models of gradient-induced cell polarization in yeast. At the core is a two-stage system consisting of a heterotrimeric G-protein sensing module and a Cdc42 responding module. I will focus on how this arrangement balances the tradeoff between amplification and tracking, and acts as a filter that attenuates input noise.

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## Ratcheting polymerase through DNA with small translocation energy bias

In gene transcription, RNA polymerase move processively along DNA to synthesize a complementary RNA strand from the template DNA. It has been suggested that the polymerase proceeds in a Brownian ratchet fashion, with its forward directionality supported not mechanically, but chemically, by nucleotide incorporation during RNA synthesis. Combining recent experimental data from single molecule force measurements with information from high-resolution molecular structures, we present a computational model dissecting details of the polymerization mechanism. From current model we notice that a small free energy bias exists in the polymerase translocation, either to serve for nucleotide selection in maintaining transcription fidelity, or to coordinate with some protein factor for certain functional control.

Erin Bodine, Assistant Professor, Rhodes College, Memphis, TN, USA
**Jize Zhang**, Rhodes College, Memphis, TN, USA

**Modeling of Measles Epidemics By Realistic Age-Structured (RAS) Approach and Examining the Effects of Vaccination Through Individual-based Modeling**

The history of measles offers a typical example on the effects of vaccination in controlling epidemics. Instead of using a SEIR model, we adopted the realistic age-structured (RAS) model, which takes into account age of children and seasonality in school years to capture the dynamics of measles. Further, we adapt the RAS model to include family networks. We simulate the result of different vaccination strategies using individual-based modeling, specifically the software Netlogo. This work is an attempt to demonstrate the effectiveness and importance of vaccination, since there are increasing unsubstantiated concerns about the side effects of vaccination and refusal of vaccination, as well as to find the most effective method of vaccination and the vaccination threshold in a community in order to prevent outbreaks.

## Title: A Mathematical Model of Schistosomiasis with Control Strategies

Author: **Ruijun Zhao**, Department of Mathematics and Statistics, Minnesota State University, Mankato

Abstract: Schistosomiasis is listed as a big worldwide health problem by World Heath Organization, the second most prevalent only after malaria in tropical parasitic diseases. Schistosomiasis is a disease caused by indirect parasite Schistosome, who spend their adult life time in the human hosts and their larva time in the intermediate snail hosts.

In this talk, we will studies the control strategies of *Schistosoma mansoni* infection with *Biomphalaria glabrata* (snails) as intermediate host and human as destination host. I will talk how to build our model, and then partially analyze the stability of the multiple equilibria, finally draw a condition and make some suggestions to the Health Department based on our model.

**Shan Zhao,** Department of Mathematics, University of Alabama, Tuscaloosa, AL, USA, 35487

## Fast Simulations of Pseudo-time Coupled Nonlinear Biomolecular Solvation Systems

In order to carry out quantitative description and analysis of various important biological processes at the atomic level, including signal transduction, DNA recognition, transcription, translation, protein folding and protein ligand binding, the analysis of the underlying biomolecular solvation is indispensible. This is because these important processes occur naturally in water, which comprises 65-90% of cellular mass. Biologically, the solvation analysis concerns with interactions between solute macromolecules and the surrounding solvent molecules or ions.

Recently, a family of differential geometry based multiscale solvation models have been developed for analysing the equilibrium properties of solvation by Wei and his collaborators. Based on the fundamental laws of physics, a free energy minimization or optimization process is conducted in these models. The total free energy functional for the solvation analysis typically consists of the electrostatic potential, the geometrical effect of the solvent-solute interface, the mechanical work of the system and the dispersive solvent-solute interaction. By using the Euler-Lagrange variation, two coupled nonlinear partial differential equations (PDEs) are derived as governing equations – one nonlinear Poisson-Boltzmann (NPB) equation for electrostatic potential and one generalized Laplace-Beltrami equation defining the solvent-solute interface or the biomolecular surface.

More recently, we have proposed a pseudo-transient continuation model for the theoretical modeling of biomolecular surface and solvation process. The major improvement of this differential geometry based multiscale model in comparison with the previous ones is a more efficient coupling of underlying nonlinear PDEs through the introduction of a pseudo-time in each process. By treating the NPB equation as the steady state solution of a time dependent process, the overall model coupling is accomplished by the explicit Euler time integration and controlled by time increments. This coupling is simpler than the relaxation based iterative procedure used in the literature, with less controlling parameters. Moreover, the NPB equation can be treated in the same manner as the linearized Poisson-Boltzmann (LPB) equation, which is impossible in conventional coupling. However, there are considerable numerical difficulties associated with the temporal discretization of the pseudo-time coupled solvation model. Such difficulties are essentially due to the nonlinear source term of the NPB equation, which involves a hyperbolic sine function of the electrostatic potential in the univalent mobile ions setting. Thus, a very small time increment has to be used in explicit Euler scheme. Moreover, instability issues are encountered for smoothly varied solute-solvent interface so that a filtering process has to be conducted.

Most recently, we have proposed to solve the time-transient NPB equation by using operator splitting based alternating direction implicit (ADI) schemes, while the simple Euler scheme is still used for the generalized Laplace-Beltrami equation. After the time splitting, the nonlinear term can be integrated analytically in the proposed algorithm, so that the overall time stepping scheme for the NPB equation is fully implicit. Thus, the proposed time splitting ADI schemes are found to be unconditionally stable for solving the NPB equation in benchmark examples with analytical solutions. Central finite differences are employed to discretize the inhomogeneous diffusion term of the NPB equation to form tridiagonal matrices in the Douglas and Douglas-Rachford type ADI schemes. The fast Thomas algorithm can thus be employed to solve the tridiagonal systems. Example solvation analysis of various compounds and proteins is carried out to validate the proposed models and algorithms. In solving the coupled system with two nonlinear PDEs, the proposed time splitting based alternating direction implicit (ADI) schemes are no longer unconditionally stable for the NPB equation. Nevertheless, the time stability of the NPB equation can be maintained by using very large time increments, so that the present biomolecular simulation becomes about ten times faster.

# Agent-based modeling and approximation for *Toxoplasma gondii* transmission dynamics in a virtual farm

**Xiaopeng Zhao**, Matthew Turner, Department of Mechanical, Aerospace, and Biomedical Engineering
Suzanne Lenhart, Department of Mathematics
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*Toxoplasma gondii* (*T. gondii*) is a common eukaryotic parasite, which can be transmitted to humans via contaminated food and water, or undercooked meat products. Up to 10% of the human population in the US and 30% in the world are chronically infected. In some regions, the prevalence can be as high as 80%. Although infection of immunocompetent people is mostly asymptomatic, the latent feature of Toxoplasmosis is a hidden danger to human health. For example, infections in humans can cause life-threatening encephalitis in immunocompromised persons such as AIDS patients, recipients of organ transplant and cancer chemotherapy. In addition, infection acquired during pregnancy may spread and cause severe damage to the fetus.

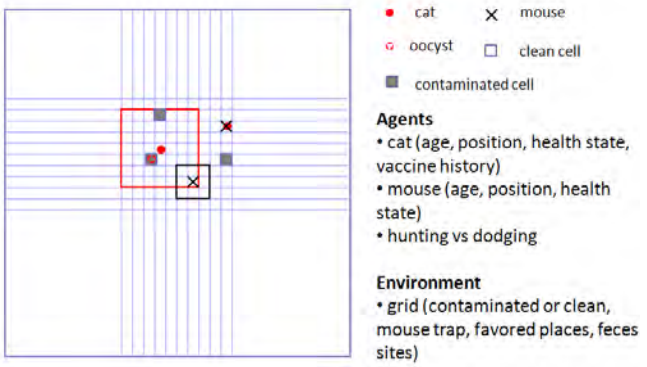


Figure 1: sketch of an agent-based model for Toxoplasma in a virtual farm.

We develop an agent-based model to describe the complex life cycle of *T. gondii* in a virtual farm. Here, an infected cat may cast feces containing oocysts of *T. gondii* to the environment. If a mouse comes into contact with an area that is contaminated with oocysts, it may ingest the oocysts and get infected. Then, a cat, ingesting the tissue cysts of an infected mouse, may become infected. A cat may also get infected from oocysts in the environment but with a much lower probability. In addition, the vertical transmission from the infected mice to their offspring is another possible route of transmission of *T. gondii*. All of the above mentioned transmission behaviors are assumed to occur with certain probabilities. For simplicity, we assume cats and mice do not migrate to and from the farm. Numerical simulations are carried out to study the efficiencies of various transmission strategies and to understand the influences of parameters. To facilitate analytical understanding on transmission strategies of *T. gondii*, we develop a spatiotemporal continuous time Markov chain model to approximate the population level dynamics of the ABM. Preliminary studies using a simplified dynamics framework show that the Markov chain model can accurately approximate its agent-based counterpart.

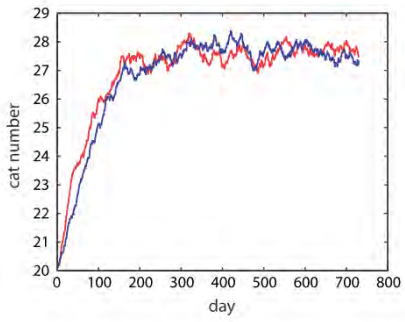


Figure 2: The average cat number over 100 simulations using ABM (red) and CTMC approximation (blue).

# A Mathematical Model for Within-host Toxoplasma gondii Invasion Dynamics

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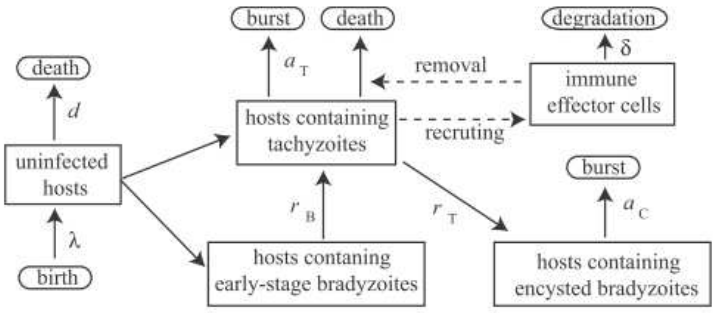
Toxoplasma gondii (T. gondii) is a protozoan parasite that infects a wide range of intermediate hosts, including all mammals and birds. Up to 20% of the human population in the US and 30% in the world are chronically infected. This paper presents a mathematical model to describe intra-host dynamics of T. gondii infection. The model considers the invasion process, egress kinetics, interconversion between fast-replicating tachyzoite stage and slowly replicating bradyzoite stage, as well as the host's immune response. Analytical and numerical studies of the model can help to understand the influences of various parameters to the transient and steady-state dynamics of the disease infection.




A compartmental model representing the dynamics of T. gondii.

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## Dispersal Limits and Climate-driven Range Shifts: an Integrodifference Equation Perspective

Climate change is causing many species to shift their ranges poleward in latitude or upward in elevation. For species with limited dispersal abilities, we naturally ask: can they keep up with climate change? How do their growth and dispersal affect their abilities to keep up with the change? In our attempt to assess the impact of climate change on population persistence, we analyze an integrodifference equation with shifting integral limits that combines growth, dispersal, and a constant-speed shift in habitat. In this talk, I will show that, for our model, the population exhibits range shifts for small shifting speeds. On the other hand, if the habitat shifts faster than a critical speed, the population goes extinct. I will also demonstrate how to use our model by applying it to an endangered butterfly species, and illustrate how the critical shifting speed depends on the net reproductive rate, the mean dispersal distance, and the shape of the dispersal kernel.

# Electrodiffusion of Lipids on Membrane Surfaces

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Lateral random translocation of lipids and proteins is a universal process on membrane surfaces. Local aggregation or organization of lipids and proteins can be induced when this lateral random diffusion is mediated by the electrostatic interactions and membrane curvature. Though the lateral diffusion rates of lipids on membrane of various compositions are measured and the electrostatic free energies of predetermined protein-membrane-lipid systems can be computed, the process of the aggregation and the evolution to the electrostatically favorable states remain undetermined. Here we propose an electrodiffusion model, based on the variational principle of free energy functional, for the self-consistent lateral drift-diffusion of multiple species of charged lipids on membrane surfaces. Finite sizes of lipids are modeled to enforce the geometrical constraint of the lipid concentration on membrane surfaces. A surface finite element method is developed to appropriate the Laplace-Beltremi operators in the partial differential equations (PDEs) of the model. Our model properly describes the saturation of lipids on membrane surface, and correctly predicts that the MARCKS peptide can consistently sequester three multivalent phosphatidylinositol 4,5-bisphosphate (PIP2) lipids through its basic amino acid residues, regardless of a wide range of the percentage of monovalent phosphatidylserine (PS) in the membrane.

## Theory of acitve transport in filopodia and stereocilia

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**Abstract:**

The biological processes in elongated organelles of living cells, such as filopodia, stereocilia, microvilli or flagella, are often regulated by molecular motor transport. The molecular motors may be an important delivery mechanism of the building material to the end of such organelle, when the organelle is too long for diffusion to be fast enough. We determined the stationary spatial distributions of motors in such organelles, corresponding to a basic scenario when motors only walk along the substrate, bind, unbind, and diffuse. Surprisingly, these stationary distributions are universal for the given set of model parameters regardless of the organelle length, which follows from the form of the kinetic equations and the boundary conditions. We developed a mean-field model, with a good quality approximate analytical solution, which quantitatively reproduces elaborate stochastic simulation results as well as provides a physical interpretation of experimentally observed distributions of Myosin IIIa in stereocilia and filopodia. The mean-field model showed that the jamming of the walking motors is conspicuous, and therefore damps the active motor flux. This damping can negate any role of motors if it requires for them to be walking far from the organelle base.

The organelle length is often set up by fluxes of building material, mostly, G-actin. Since the motor distributions are decoupled from the lengths, it is straightforward to build a theory of active transport of G-actin monomers by this motors and solve it as a separate problem with motors distributions as external field. Corresponding G-actin distributions in the organelle define its length. We found that the concentration profile of G actin along the filopodium is rather nontrivial, containing a narrow minimum near the base followed by a broad maximum. For efficient enough actin transport, this nonmonotonous shape is expected to occur under a broad set of conditions. The maximum in G-actin concentration appears before the motor jam and effectively increases the concentration gradient for diffusion of G-actin towards the tip. The increase in the gradient is enough to speed up the diffusion to allow for severalfold longer filopodia. Thus the main role of transport is in locally bumping up the concentration to speed up the diffusion rather than to actually carry the monomers all the way to the tip.