ANNUAL REPORT DMS-1440386: YEAR 2017-2018

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INTRODUCTION

The Mathematical Biosciences Institute (MBI) is a multi-disciplinary initiative that facilitates interaction between the mathematical sciences (which includes mathematics, statistics, and computations) and the biosciences (which includes the biological sciences, medical sciences, and environmental sciences, which relate to the living world). The Institute is devoted to the mathematical biosciences, which includes all areas of research in bioscience where participation of the mathematical sciences will lead to important progress. MBI offers a vigorous program of research and education, and fosters the growth of an international community of researchers in mathematical biology.

MBI MISSION STATEMENT

The mission of MBI is:

- To foster innovation in the application of mathematical, statistical, and computational methods in the resolution of significant problems in the biosciences;
- To foster the development of new areas in the mathematical sciences motivated by important questions in the biosciences;
- To engage mathematical and biological scientists in these pursuits; and
- To expand the community of scholars in mathematical biosciences through education, training, and support of students and researchers.

To support this mission, MBI programs are designed to reinforce and build upon existing research efforts in the mathematical biosciences, and to inspire and accelerate the expansion of the community and its intellectual growth. These include emphasis year programs, current topic workshops, education programs, and research projects. The administrative and governance structure of the MBI are designed to support the mission of the Institute.

MBI VISION STATEMENT

The vision of the Mathematical Biosciences Institute is:

- To be a national center for the Mathematical Biology community; a place where all researchers with connections to mathematical biology seek to participate.
- To be the premier center for postdoctoral training in mathematical biology.
- To be the central hub that motivates and facilitates the mathematical sciences and the life sciences communities to create, share, and respond to research and educational opportunities

MBI DIVERSITY STATEMENT

The MBI diversity mission is to help shape the mathematical biology community in a way that represents the diversity of our society. Historically, women, African-Americans, Hispanics, Native American, and Alaskan Natives have been underrepresented in the mathematical biology community. MBI will work at two levels. First, it is MBI policy that each of its programs should actively seek diversity among its participants in gender and ethnicity. Second, MBI will sponsor activities that promote mathematical biology and its opportunities in the academic community. To be most effective, these activities should reach the undergraduate and pre-college levels, and contribute to increasing the diversity of future mathematical biologists. The Diversity Committee

helps MBI to carry out this mission.
Specifically, MBI will build and maintain diversity by the following:

- **Boards and Advisors:** Ensure representation of underrepresented groups among the Directors, the Board of Trustees, the Scientific Advisory Committee, and the Local Scientific Advisory Committee
- **Science Workshops and Emphasis Programs:** Include members of underrepresented groups as members of emphasis year and workshop organizing committees and ensure broad representation among workshop participants.
- **Training of Younger Scientists:** Ensure broad representation among postdoctoral fellows and build exposure of younger scientists to mathematical biology.
- **Awareness Workshops:** Periodically host workshops on Opportunities in Mathematical Biology for Underrepresented Groups The first of these workshops occurred in 2007.

In addition, MBI pursues the following strategies:

- Participate in meetings of minority scientists, such as the Society for Advancement of Chicanos and Native Americans in Science (SACNAS) and the Historically Black Colleges and Universities Undergraduate Program (HBCU-UP), to provide information about MBI, recruit participants to MBI activities, and inform young scientists about opportunities in mathematical biology.
- Build relations with academic institutions having strong minority enrollments.
- Advertise MBI programs both broadly and to targeted audiences, including meetings of mathematical biology societies and minority-serving science societies.
- Evaluate the implementation of the MBI diversity plan annually.

SUMMARY OF MBI PROGRAMS IN ACADEMIC YEAR 2017-2018

MBI hosted two Emphasis Semester programs in 2017-2018: the autumn 2017 Emphasis Semester was on *Control in Biology and Medicine* and the spring 2018 semester was on *Infectious Diseases: Data, Modeling, Decisions.*

Autumn 2017 Emphasis Semester: Control in Biology and Medicine

The Organizing Committee for the **Autumn 2017 Semester** consisted of **German Enciso (**Mathematics, UC Irvine), **Pablo Iglesias (**Electrical & Computer Engineering, Johns Hopkins University), **Jeff Moehlis** (Mechanical Engineering, UC Santa Barbara), Mette Olufsen (Mathematics, NC State), **Peter Thomas (**Mathematics, Applied Mathematics, and Statistics, Case Western Reserve)

The traditional boundaries between mathematics, engineering, and the life sciences are rapidly blurring as interdisciplinary researchers develop new tools and adapt existing methods to explore fundamental questions and practical problems in biology and medicine.

Approaches from control theory are having a growing impact on the study of biological systems and the development of new medical applications. This includes considering how a system's dynamical behavior is influenced by inputs and feedback, for instance how to design such inputs to achieve the desired outcomes even in the presence of uncertainty, heterogeneity, and noise. Depending on the problem of interest, techniques from one or more of the following sub-areas of control theory may be important: linear systems theory, nonlinear control, robust control, hybrid

control, optimal control, stochastic control, system identification, optimization, estimation, and filtering. This emphasis semester focused on three broad areas for which the methods of control theory have already shown particular promise and are expected to continue to make significant contributions:

Workshop 1 was on the control and modulation of neuronal and motor systems. This included the study of rhythmic activity patterns in the brain that underlie essential functions such locomotion, respiration, and circadian activity, or which arised in pathological situations such as epilepsy and Parkinson's disease. The workshop also encompassed control of non-oscillatory motor behaviors such as maintaining posture and generating specialized non-repetitive movements.

Workshop 2 was on the control of cellular and molecular systems. This included the use of control theory to understand and modulate gene expression and cell signaling. It also considered synthetic biology, which was the design of cellular regulatory systems to accomplish desired outcomes.

Workshop 3 was on the control of disease using personalized medicine. This addressed how control theory, particularly system identification and robust control, could be used to overcome the challenges of designing drug- and device-based medical treatments given the individual variability within a patient population.

Workshop 4 was on sensori-motor control of animals and robots. Humans and other animals still typically outperform robots in many movement tasks -- in versatility, stability, robustness, and energy consumption. How do humans and other animals achieve such performance? This workshop was attended by researchers studying humans and non-human animals and those that try to build robots, performing movements of different types.

The workshops brought together control theorists, applied mathematicians, experimental biologists, and clinicians to share ideas and to report on the challenges that they would face in investigating various important biological and medical applications. It would also be a chance for new collaborations to form, which would help to further blur the traditional boundaries between mathematics, engineering, and the life sciences.

Autumn 2017 Emphasis Semester Workshops

1. 3rd Workshop on Omics Data Analysis (September 05 - 07, 2017)
2. Workshop 1: Control and Modulation of Neuronal and Motor Systems (September 11 - 15, 2017)
3. Workshop 2: Control of Cellular and Molecular Systems (October 02 - 06, 2017)
4. Workshop 3: Control of Disease: Personalized Medicine Across Heterogeneous Populations (October 30 - November 03, 2017)
5. Workshop 4: Sensori-motor control of animals and robots (November 13 -17, 2017)

Spring 2018 Emphasis Semester: Infectious Diseases: Data, Modeling, and Decisions

The Organizing Committee for the **Spring 2017 Emphasis Semester** on *Infectious Diseases: Data, Modeling, and Decistion* consisted of **Carlos Castillo-Chavez** (MCMSC, Arizona State), **Carolyn Cho** (Quantitative Pharmacology & Pharmacometrics, Merck, Sharp & Dohme), **John Drake** (Odum School of Ecology, University of Georgia), **Alan Perelson** (Theoretical Biology and Biophysics Group, Los Alamos National Laboratory), **Larry Schlesinger** (Center for

Microbial Interface Biology, The Ohio State University), **Joe Tien** (Mathematics, The Ohio State University), and **Pauline van den Driessche** (Mathematics and Statistics, University of Victoria)

The effectiveness of improved sanitation, antibiotics, and vaccination programs created a confidence in the 1960s that infectious diseases would soon be eliminated. As a result, chronic diseases such as cardiovascular disease and cancer started to receive more attention in the United States and industrialized countries. But infectious diseases have persisted and have continued to be the major causes of suffering and mortality both in developing and industrialized countries. As the infectious disease agents adapted and evolved, new infectious diseases have emerged (dengue fever in 1945, HIV in 1981, hepatitis C in 1989, hepatitis E in 1990, SARS in 2002, novel H1N1 influenza strain in 2009) and some existing diseases have recently reemerged (Zika). Antibiotic-resistant strains of tuberculosis, pneumonia, and gonorrhea have evolved and are becoming of major concern today in many parts of the world. Malaria, dengue, and yellow fever have reemerged and are spreading into new regions as climate changes occur. Diseases such as plague, cholera, and hemorrhagic fevers (Ebola, Lassa, Marburg, etc.) continue to erupt and occasionally reach dangerous thresholds of global pandemics, with the Ebola outbreak of 2014 originating in West Africa providing a recent example.

The emerging and reemerging diseases have led to a revived interest in infectious diseases, with mathematical and computational models becoming essential tools in analyzing their spread and suggesting possible mechanisms for control. Indeed, it is widely believed that better understanding of the transmission characteristics of infectious diseases at various temporal and physical scales, for instance in host-pathogen interactions, host tissues, interactions between individuals, communities, regions, and countries will lead to better approaches to decreasing the transmission of such diseases. This understanding can be greatly enhanced by the mathematical modeling effort which allows to clarify assumptions, variables, and parameters and to provide conceptual results such as thresholds, basic reproduction numbers or contact and replacement numbers. At the level of host-pathogen interactions, the mathematical models may answer questions about specific behavior of the immune systems relevant to developing effective vaccines. At the levels of individuals, the complex data from social networks may be used to build models predictive of human behavior in the face of global pandemic events. At the level of populations, the models of environmental changes may help us better understand the challenges associated with habitat loss and changing climate patterns. In order to integrate the diverse data at different scales, the multiscale mathematical models can be designed to create testable hypotheses leading to new investigational studies, identify and share gaps in knowledge requiring further research, uncover biological mechanisms, or make predictions about clinical outcome or intervention effects. These models can draw on a variety of modern information resources including relevant physical, environmental, clinical and population data. To address these numerous challenges, the scientific program at MBI consisted of four workshops focusing at the crucial areas of modeling modern infectious diseases born.

Workshop 1 was on infection and immune response modeling, particularly within tissues, has gained increasing prominence in the research agenda. Modeling, combined with experimentation, is answering important questions about health and disease biology, biomarkers, and therapeutic and vaccine intervention. Experimental advances in interrogating the adaptation of infectious agents within the host as well as the host immune response are generating large and complex datasets. These data create mathematical challenges in understanding the newly observed

phenomena and making predictions regarding the underlying mechanisms and networks.this area will lead to new developments in applied mathematics techniques (for example, previous models in these areas have led to interesting developments in applied stochastics and applied dynamical systems research).

Workshop 2 was on the integration of social and biological theory, which is particularly poignant in the context of epidemics, where the dynamics, control, and evolution of communicable and vector-borne diseases are intimately connected to the joint dynamics of epidemiological, behavioral, and mobility processes that operate across multiple spatial, temporal, and organizational scales. It is therefore important to identify and quantify the individual-level processes responsible for observed epidemiological patterns: the result of individual interactions in changing social and ecological landscapes, which includes the construction of an encompassing theoretical explanatory framework that can identify the limitations of existing theory. This workshop sought out to disentangle the role of epidemiologic and socioeconomic forces on human disease dynamics.

Workshop 3 discussed the 2014 West Africa Ebola outbreak and the arrival of Zika underscore the spatio-temporal ecological factors that influence disease dynamics. Disease ecology has been a very fruitful area for collaboration between theoreticians and experimentalists, and the relevance for public health is apparent with concerns of zoonotic and vector borne diseases, interconnectedness between different communities at several scales, pathogen resistance, and the impacts of climate change, habitat fragmentation, and biodiversity loss on disease dynamics. These challenges call for novel data collection and usage, as well as new mathematical models and theoretical results. The aims of this workshop was to bring together researchers working in these different areas, in order to stimulate collaboration and discussion, with the goal of informing possible effective public health interventions.

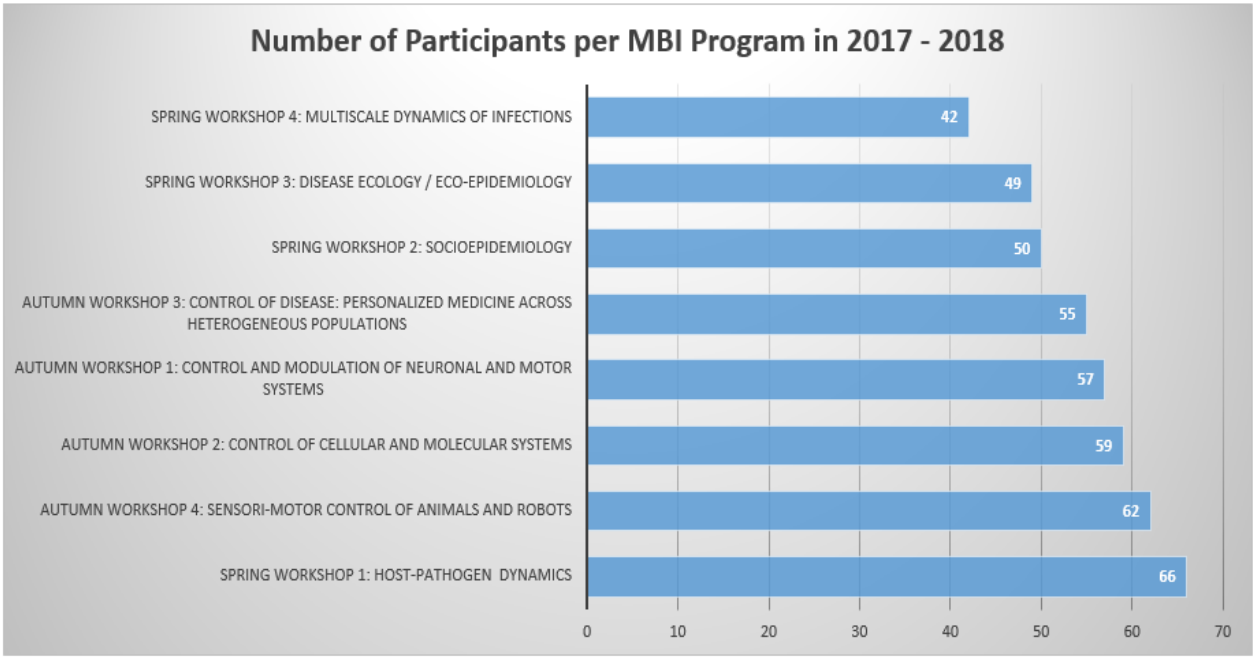
Workshop 4 deliberated on modern methods of genomic data collection reveal a great heterogeneity and diversity among strains of pathogens with different genotypes infecting hosts with significant differences in virulence, immunogenicity, and antigenic variation on a micro-scale (Workshop 1). The presence/persistence of specific different sub-groups of such pathogens depends heavily on macro-scale interactions of various human and animal hosts, travel patterns, environment, and intervention strategies (Workshop 2-3). In order to properly understand the main drivers of transmission of infectious disease, these ecological, molecular, and immunological factors need to be analyzed together, and their joint correct characterization requires a comprehensive interdisciplinary and multi-scale modeling approach. We expect that different infection outcomes are the result of the interplay of events at organ tissue cellular and molecular as well as ecosystem scales over the time course of minutes to years.

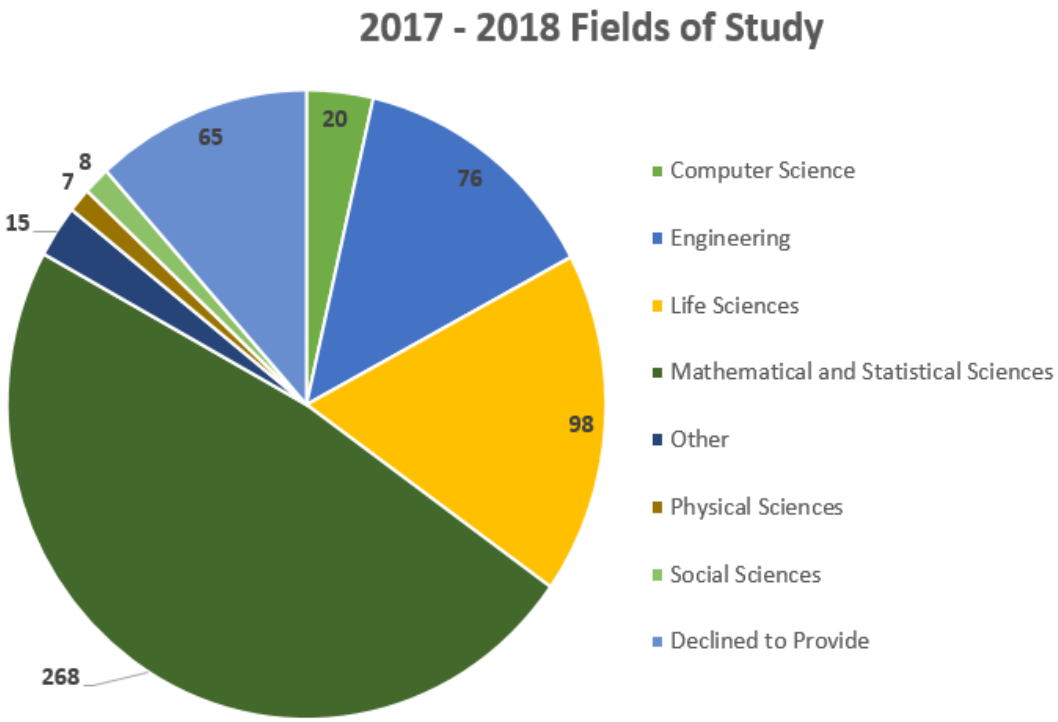
Spring 2018 Emphasis Semester Workshops

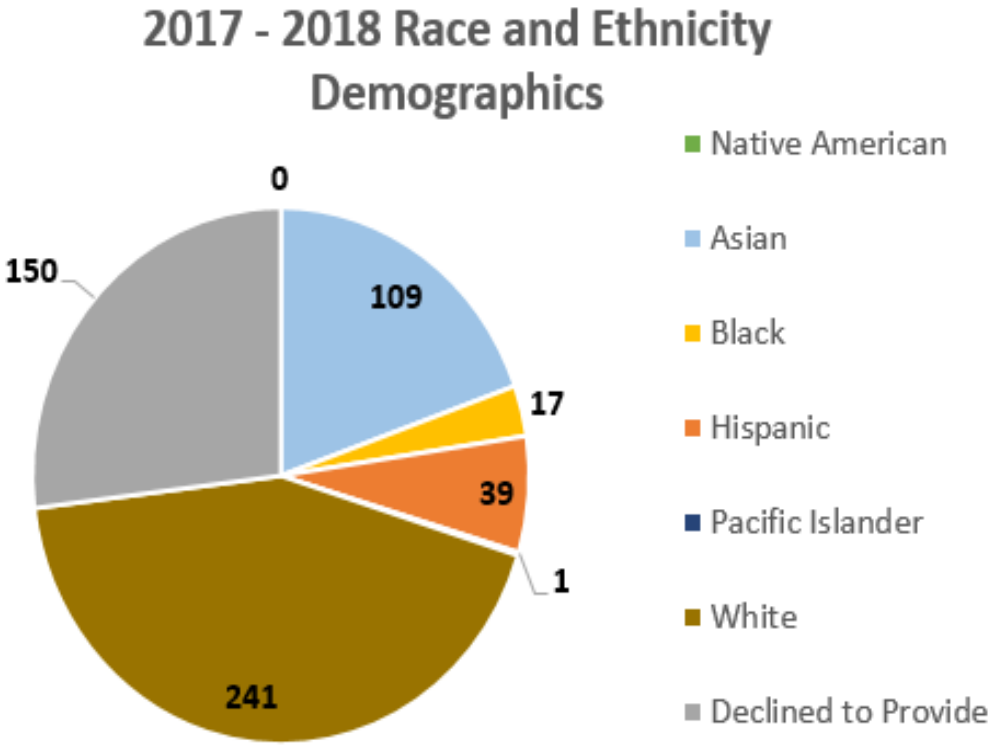
1. Workshop 1: Host-Pathogen Dynamics (February 19 - 23, 2018)
2. Workshop 2: Socioepidemiology (March 05 - 09, 2018)
3. Workshop 3: Disease Ecology/Eco-epidemiology (March 26-30, 2018)
4. Workshop 4: Multiscale Dynamics of Infections (April 23 -27, 2018)

PARTICIPANT DATA & DEMOGRAPHICS

-557 participants, mentors and speakers took part in MBI's 2016-2017 Programs.
-A complete list of participant data is attached in the "Accomplishments" section of the research.gov online reporting form.



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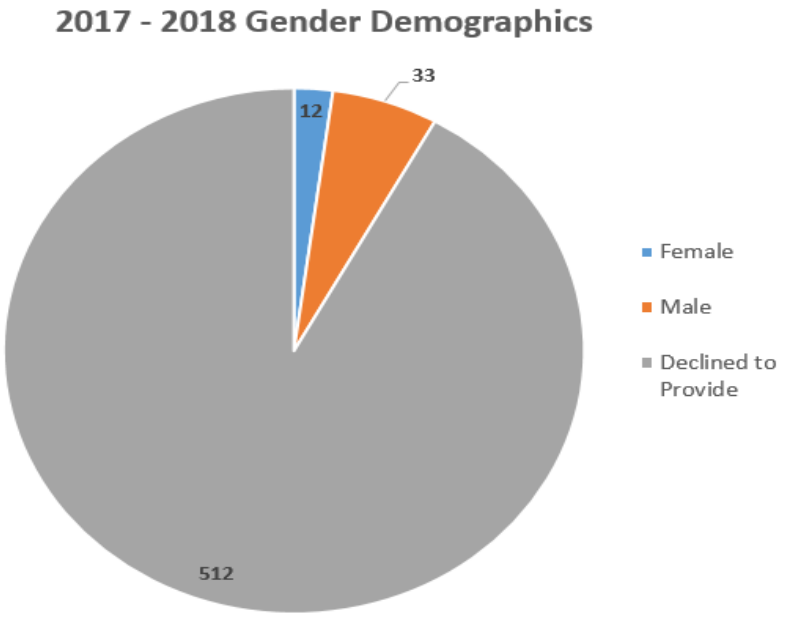
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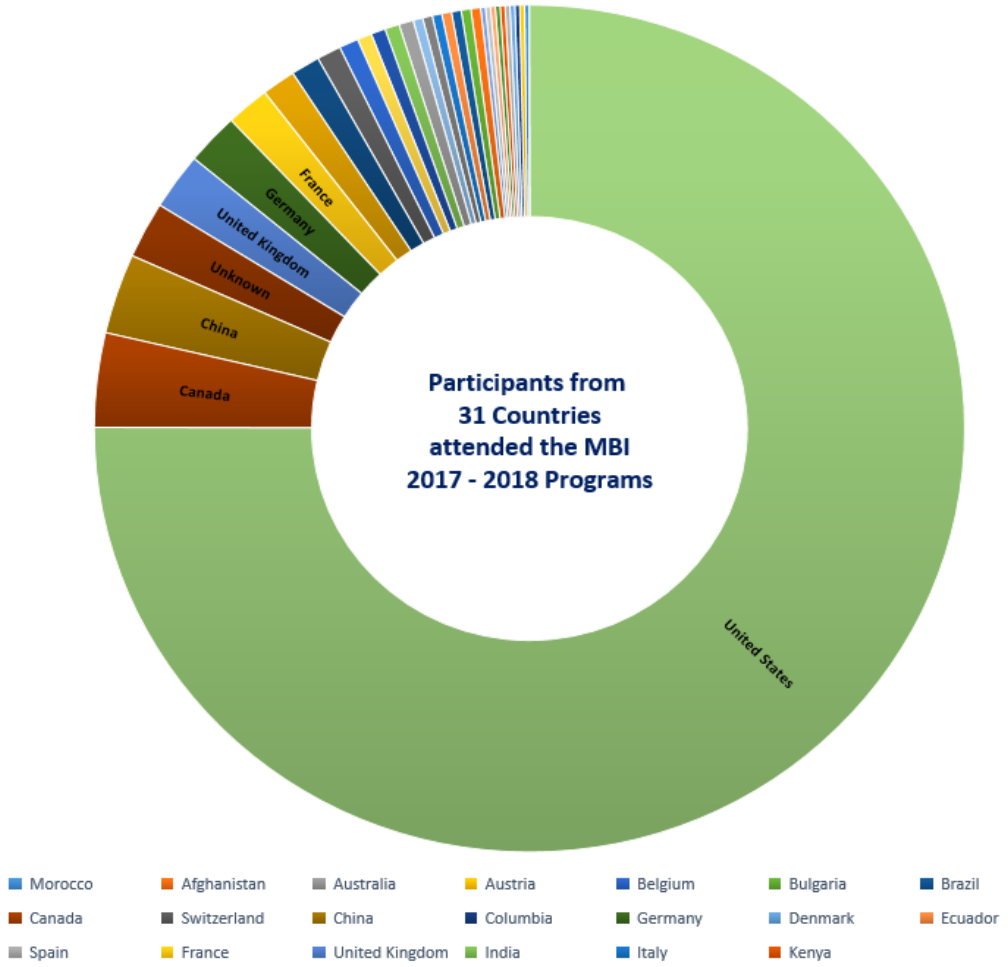
Declined to Provide



WORKSHOP REPORTS

Autumn Workshop 1 - Modeling and Inference from Single Molecules to Cells (September 11-15, 2017)

MONDAY, SEPTEMBER 11, 2017

Physics of protein folding and its relation to evolution and cellular laws
Kenneth Loparo (Case Western Reserve University)
Dr. Loparo began his talk with an overview emphasizing how input-output systems would be the basis for the results that would be derived on linear systems. To make it clear the types of systems that would be considered, the speaker gave many examples of input output systems. These examples included but were not limited to dynamical systems with the cases: linear, non-linear, time-invariant, and memoryless. The first example of a single input-single output (SISO) system involved the Dirac generalized function as it was computationally tractable and the system possessed the aforementioned properties. A key result was considering point-to-point steering of a linear time invariant systems translated into a classic controllability problem for the underlying system. After developing the SISO case thoroughly, Dr. Loparo moved to the multiple input-multiple output (MIMO) case and observability. The speaker ended with an overview of the linear

quadratic regulator, which was formulated a convex optimization problem. He showed that the optimal solution is a product of factors including coefficients for the input, the state vector, and a term that solves the Algebraic Riccati Equation.

Feedback, sensitivity, and excitability
Rodolphe Sepulchre (University of Cambridge)
This tutorial aimed to address the control and modulation of rhythmic behaviors encountered in biology. There was a particular emphasis on experimental questions from neurophysiology. This discipline benefits from a matured modeling framework grounded in circuit theory, a key historical bridge between input-output and state-space modeling. The tutorial focused on the mathematical question of whether a tiny control could stabilize a large system in the presence of uncertainty. The speaker gave the example of the construction of the non-inverting amplifier to and how the addition of a resistance wire is effectively the introduction of a control. Given the time before mathematical tools were available to study this amplifier also served to emphasize the daunting gap between the concepts of feedback, sensitivity, and excitability and the mathematical modeling framework. To emphasize the need for sensitivity analysis, the speaker considered high-dimensional models of dopamine levels in neurons. In these models the addition of feedback via new conductance paths was analogous to the addition of resistances in the amplifier. A takeaway message the speaker wanted to provide was that "Feedback alters the meaning of a model, but not the function." To make the point of sensitivity of neuronal signaling, differences in model output with and without open-loop and closed-loop control were explored.

Oscillopathies: From Squid Axons to Infant Apneas
David Paydarfar (University of Texas - Austin)
The speaker began with examples of neuronal oscillations in both healthy and diseased states. Oscillations during diseased states include tremors, nystagmus, epilepsy, and, the biological focus of this talk, infant apneas. The central question of the work presented was how does connectivity determine neural behavior. A key aspect of the work presented required considering the geometry of oscillators. In the case of voltage dynamics in a squid giant axon, there are circular limit cycles about a stable steady state that are noise-resistant since it would take an external stimulus current to move from the outer stable limit cycle to the steady state. Whereas in the case of infant apnea, it was shown by the speaker that the outer stable limit was irregular and it was possible to predict the timing of external stimulus current that will push neuron to a stable steady state. To conclude the speaker showed experimentation that simulated "instinctive resuscitation of the newborn", tactile stimulation to stimulate breathing, and dynamically this serves to keep infant breathing on the stable limit cycle.

Eupnea, Tachypnea, and Autoresuscitation in a Closed-Loop Respiratory Control
Casey Diekman (New Jersey Institute of Technology)
The motivation for this talk was the common challenge facing biological processes: adaptive regulation of central pattern generator (CPG) activity. The speaker used the Butera-Rinzel-Smith model for pre-Botzinger Complex neurons to simulate CPG activity. He found that embedding the CPG model into a respiratory control loop created a bistable system that was capable of sustained normal breathing as well as pathological rhythms. Moreover, it was determined that the mechanisms that produced normal bursting oscillations in the closed-loop system were different than the bursting oscillations mechanisms in a model with open loop control. The chemosensory feedback made the model with closed-loop controls more robust to changes in metabolic demands

and, in particular, more so than the open-loop model. Finally, the CPG model provided a mechanism for autoresuscitation for recovery from transient interruption of chemosensory feedback.

Optogenetic vs. electrical stimulation of synchronized oscillations in a computational model of parkinsonian basal ganglia
Leonid Rubchinsky (Indiana University-Purdue University Indianapolis)
The talk focused on the suppression of neural synchronization in pathological situations. The speaker began with a review of how neural oscillators can become entrained and stated a variety of neural processes that require synchronization before moving toward the the biological focus of Parkinson's disease. Deep brain stimulation is often used to limit rhythms associated with involuntary movements. Comparatively, in the optogenetics the delivered stimulation is dependent on neural activity. The two feedbacks were modeled computationally and compared. It was found that electrical electrical stimulation and optogenetic excitation have somewhat similar effects. In particular, weak intensities may slightly enhance pathological activity and stronger stimulations desynchronize and suppress activity. Optogenetic inhibition reduced spiking and bursting activity, though strong stimulation removed all spiking behavior. The speaker hypothesized that activity-dependent photocurrent in optogenetic stimulation could be an adaptive form of deep brain stimulation in the future based on the modeling predictions.

TUESDAY, SEPTEMBER 12, 2017

Modeling Practices for Control - a Model Predictive Control (MPC) Tutorial
Robert Parker (University of Pittsburgh)
This tutorial was focused on the situation where a model is developed and used to solve a real-time control problem involving said model. The practical biomedical example provided by Dr. Parker was how to develop an insulin pump that can be controlled in a closed-loop setting to register insulin levels and deliver necessary doses to diabetic patients. The speaker provided examples of both data-driven and mechanistic models to show that linear model-predictive control is often effective in computational and analytical problem formulations, but limitations in the model can affect performance in the closed loop case. Dr. Parker finished by considering nonlinear systems modeling since behaviors like step responses are more applicable. The associated optimal control problem in the nonlinear case was asymmetric to reflect different penalizations for extreme values of the objective; rephrased in terms of the applications, the insulin pump should behave differently in the cases when glucose was too high or too low.

Nonlinear Filters for the Linearly-inclined
Terence Sanger (University of Southern California)
The speaker began this tutorial by motivating filtering problem of using limited samples to choose a plausible state of a system from a pre-specified set. Moreover, he stated that the specific application would be estimating intended movements from cerebral palsy patient EMGs. Before moving to the biological application, the speaker sought to build the necessary mathematical framework in several steps, starting with linear filtering and then moving towards continuous and discrete nonlinear filtering. Broadly, the filtering procedure required a prediction, a subsequent measurement, and an update to the probability distribution on the state space. In the case of linear filtering, the process of measuring and updating dynamics alternated. To illustrate the linear case, he gave the example of a Kalman filter. In the nonlinear case, updates to dynamics and

measurements were summed and this led to a stochastic differential equation (SDE). Using the Feynman-Kac lemma, the forward propagation step represented by this SDE was able to be related to a linear partial differential equation. The speaker further illustrated with the example of a particle filter, a discrete-time Bayesian filter. In the continuous case, the speaker's group had developed a new algorithm using a general stochastic measurement model, that gave more accurate predictions than the existing Kushner method. The choice of measurement model in this new method links information theory and signal processing.

Localized negative conductance: a general modelling principle for behaviors across scales
Alessio Franci (National Autonomous University of Mexico)
In his presentation, Dr. Franci explained the concept of negative conductance and its relevance to multi-scale dynamical behaviors. He began with the definition of the negative conductance and pointed out the historical evidences of it back in early years of twentieth century. Next he explained the "voltage clamp" experiments performed by Hodgkin and Huxley and the appearance of fast negative conductance in such experiment. He further described the equivalence between negative (positive) conductance and positive (negative) feedback.

The main message of the talk was that slow negative conductance (feedback) is necessary and sufficient for robust and tunable modelling of bursting, e.g. neuronal bursting. Therefore, by modulating a few feedback loops that combine the dynamic response of neuronal ionic currents, one can create regions of negative conductance that are responsible for neuronal switching and oscillatory behaviors leading to bursting. Finally, he illustrated that how by changing the amount of positive and negative feedback we can get modulation and robustness at any number of scales. This helps to model "bursts of bursts" phenomena like circadian rhythms.

Stability requirements and benefit of multiple forms of neuronal homeostasis
Paul Miller (Brandeis University)
When more than one homeostatic process is at work in a given system, there is always a chance the two will compete with each other. Dr. Miller started his presentation with a physical example of such systems in which two thermostats in a room control different heating/cooling systems. Unless their set-points are identical, one could be causing heating and the other cooling while the temperature lies intermediate between the two set-points. In neurons, multiple homeostatic mechanisms appear to be at play. In his talk, Dr. Miller focused on two categories, synaptic scaling, which impacts connection strengths between neurons, and intrinsic homeostasis, which impacts the excitability of neurons. He delineated criteria for the two homeostatic mechanisms to cooperate and produce a stable state of time-averaged neural activity. He showed that in these conditions the neuron can respond to stimuli more reliably, because the variance as well as the mean of its firing rate can be controlled with two sensors. Finally, he demonstrates that within a recurrent feedback circuit, a useful computational operation--temporal integration of inputs--can be achieved by these dual control mechanisms operating together, i.e., they robustly achieve the fine-tuning of the circuit that is necessary.

Force encoding in muscle spindles - implications for sensorimotor control of balance
Lena H. Ting (Emory University and Georgia Institute of Technology)
Dr. Ting talk was about her research on balance control of the body while it reacts to external perturbations. She illustrated the body response chain to an external perturbation using a "shifting frame" experiment and emphasised on the importance of proprioceptive sensory information to

movement. Her finding shows that rapid increase in resistive force of a passive muscle when stretched, i.e. short-range stiffness may cause enhanced sensory signals that facilitate the detection and predictive response to sudden mechanical perturbations to the body. Importantly, this history-dependent property of muscle spindle firing rates does not have a unique relationship to muscle length or velocity, but rather can be predicted in fine detail based on a unique pseudo-linear transformation between muscle force and the first time derivative of force, dF/dt and muscle spindle afferent firing rate. Several history-dependent features of muscle spindle firing rates can be predicted based on muscle force and dF/dt and are likely due to cross-bridge cycling kinetics in muscle fibers. She pointed out that such history-dependence is lacking in current models of muscle spindles, but could be necessary to explain a number of phenomena from postural response to perturbation, spasticity, and perception of limb position. Moreover, the encoding of force as a proxy for length in muscle spindles has many implications for normal and impaired control of movement. She concluded with elaboration on the implication of her finding for understanding posture preference of Parkinson patients.

Virtual Reality Alteration of Visual Feedback in Cerebellar Patients Can Improve Reaching
Amanda Edwards (Johns Hopkins University)
Dr. Edwards presented results from studying patients with movement disorder because of damage to their cerebellum. The goal of the project is to improve the movement of patients by treating them as a control system and altering their visual input. People with damage to their cerebellum often exhibit "reaching ataxia", or misdirected, poorly scaled movement patterns which are reminiscent of a poorly tuned control system. Ataxia affects almost all activities of daily living (e.g. eating, cooking, bathing, dressing, working). It is believed that these patients have a static, miscalibrated internal model of their body dynamics; however, it is unknown whether their feedback control is intact. In her work, Dr. Edwards and her colleagues have challenged these participants with visuomotor system identification tasks in order to model their feedback control architecture. Their findings suggest that cerebellar patients have intact feedback control, but are forced to rely on time-delayed visual feedback. The key difference is that healthy subjects seem to be able to compensate for their visuomotor delay suggesting that the cerebellum may be serving the role of a Smith predictor for this task. Finally, they have leveraged the cerebellar patients' intact visuomotor feedback control system to improve the scaling of these movements by altering their visual feedback based on their real-time movement in a virtual reality environment.

WEDNESDAY, SEPTEMBER 13, 2017

Adaptive locomotion control: modeling the interplay between central pattern generators and sensory feedback using mathematical models and robots
Auke Ijspeert (Ecole Polytechnique Federale De Lausanne)
Animal locomotion is amazing in its agility and diversity. There are four essential ingredients in animal motor control consisting of central pattern generators (CPGs), reflexes, descending modulation from higher control centers and musculoskeletal systems.

In this talk, Dr. Ijspeert used robots and mathematical models of the spinal cord to investigate the locomotion control in vertebrate animals, from lamprey to human. There has been a long debate between the importance of CPGs versus sensory feedback in motor control, only modeling can help us clarity their roles. Dr. Ijspeert specifically focused on the interaction between CPGs and sensory feedback to investigate their respective roles in gait generation. He also showed that many aspects

of swimming can be driven purely by sensory feedback mechanism, however, it is still worth adding a CPG to the sensory-driven network to help improve the control of speed and the robustness against sensory noise. In the end, Dr. Ijspeert discussed how the respective roles of CPGs and sensory feedback have possibly changed during evolution.

Understanding Lamprey Locomotion Using an Interdisciplinary Approach
Kathleen Hoffman (University of Maryland Baltimore County)
Lamprey locomotion involves electrical signal in the central nervous system, to the force generation of the muscle, to the interaction between the body and the environment, and to the proprioceptive feedback from sensory organs called edge cells that can modulate the rhythm of the electrical signal in the spinal cord.

Modeling and understanding this set of complex system will then require an integrated interdisciplinary approach. In this talk, Dr. Hoffman described their modeling work that consists of coupled oscillators representing the central pattern generator for locomotion, a muscle model for force generation, and a fluid-elastic body interaction that simulates lamprey swimming in the fluid environment. Finally, she made this lamprey swimming model a closed-loop system by adding sensory feedback from the edge cells that are active when the body bending occurs.

Stochastic Dynamic Operators
Terence Sanger (University of Southern California)
What happens when neuron fires? The global behavior of neurons is determined by the statistical behavior of each individual neuron. Instead of using stochastic differential equations, Dr. Sanger worked with equivalent partial differential equations (PDEs) associated with probability densities over states. These PDEs are linear with constant Jacobian matrices that are denoted as stochastic dynamic operators (SDOs) with properties of column sums being 0 and diagonal entries being negative. Using a pendulum example, Dr. Sanger showed that a single matrix operator can actually describe the full dynamics, making SDOs a very powerful tool. More than that, weights (for example, in a neural system, weights could be determined by the firing rates of neurons) can be superposed to a SDO because operators are linear and additive. SDOs implement feedback, but a closed-loop control requires weights to be dependent of states and linear combination of operators to be determined by the tuning curves of neurons. Next Dr. Sanger showed a variety of things we can do with SDOs including sequential control, feedback control, distributed implementation, distributed learning rule, spiking neuron implementation and GPU implementation. Finally, Dr. Sanger showed some interesting applications such as extraction of SDOs from Rybak model of frog spinal cord central pattern generator. Specifically, SDOs can represent effect of spiking on changing in EMG and combined network of SDOs will then predict temporal pattern of EMG.

A normative approach to motor control networks
Max Berniker (University of Illinois at Chicago)
Animals' motor behaviors are generated by animals' nervous systems, however, only a small fraction of neurons responsible for movement can be observed. To study motor control, both motor behaviors and neural activity will need to be examined in order to infer underlying processes that generate movement and to infer processes of motor control, respectively. The focus of this work is to bridge the gap between the neural processes of motor control and the resulting behavior. In this talk, Dr. Berniker introduced a normative approach to motor control networks. Specifically, he used this approach to examine the properties of a spiking network that is designed to test candidate control

processes for point-to-point reaching movements and generate testable predictions for both neural activity and motor behaviors. He performed various analyses on the network to reveal that the average activity of many neurons varies with reach directions, oscillatory activity emerges for point-to-point reaches, and so on. Finally, Dr. Berniker suggested that this approach can be used to analyze candidate hypothesis for the processes that generate movement and link observed neural behavior with motor behavior.

Two-stroke relaxation oscillators
Martin Wechselberger (The University of Sydney)
During his talk, Dr. Wechselberger tried to answer questions about origin of rhythmic patterns. He mainly challenged the necessity of the popular cubic-shaped characteristic for observing relaxation oscillations. Obviously, the negative conductance is necessary but as he claimed there is no need for two positive branches and only one should suffice. This idea brings us to two-stroke oscillators which has been originally studied in electrical engineering literature. The first two-stroke oscillators were introduced in 60s where the characteristic linearly decreases on left half-space and exponentially increase on the right one to produce slow-fast relaxation cycle. Dr. Wechselberger introduced a simpler two-stroke oscillator where the exponential term in the characteristic is replaced with a rational term. Interestingly, the oscillator still has the same desired characteristics of the original two-stroke oscillator while being simpler. He then discussed an application of two-stroke oscillation with rational term in modelling the stick-slip phenomena observed in friction. Finally, Dr. Wechselberger elaborated on the mathematical method behind his analysis of the proposed two-stroke oscillation which proves existence of a unique relaxation cycle.

Transient neural dynamics: integrating models and novel experimental paradigms
Pablo Varona (Universidad Autónoma de Madrid)
Many brain functions, from motor control to cognitive activity can be seen as built from transient sequential dynamics. This sequential switching dynamics may have as an origin a winnerless competition among different brain elements. Dr. Varona introduced a novel theoretical formalism based on heteroclinic networks which describes such dynamics and provides insight for the interpretation of many experimental results. He emphasized that closed-loop technologies have an enormous potential to precisely control the spatiotemporal aspects of a stimulus and to build activity-dependent stimulus-response loops to interact with neural systems and control them in a millisecond time scale. His results suggest that establishing these loops is an essential step towards understanding the dynamics of transient neural processes and bridges between traditionally disparate levels of analysis.

Cellular control of network rhythmic activity
Guillaume Drion (University of Liège)
Dr. Drion opened up with the question of effect of cellular activity on network rhythm. Nervous system functions are regulated by fast and localized modulation of neural network rhythmic activity. This feature is conserved amongst very different systems, ranging from invertebrate central pattern generators to mammal midbrain and cortical structures. These systems however strongly differ in their structure, function and physiological properties, and are regulated by a large number of interconnected mechanisms, which makes the extraction of key players in the robust regulation of rhythmic activity an arduous task. He introduced a cellular dynamical property called slow regenerativity from which robust and tunable modulation of rhythmic activity can emerge in many different systems, both at the cellular and network levels. Dr. Drion discussed the ubiquity of

slow regenerativity for the control of nervous system activity and illustrated its significance through several key physiological examples like network rhythm in wakefulness and sleep.

THURSDAY, SEPTEMBER 14, 2017

Special Role of the Hyperdirect Pathway in Parkinsons Disease and Deep Brain Stimulation
Cameron McIntyre (Case Western Reserve University)
The speaker began with a biological review featuring coronal pictures of the brain to use the regions that are targeted during Parkinson's disease. The origin of the pathological rhythms during Parkinson's are often associated with cells in subthalamic nucleus (STN) with a frequency in the beta band (12-20 Hz). Therapeutically, local field potentials have been used to send deep stimulations to the STN region of the brain. The speaker showed comparisons of the effects of therapeutic deep brain stimulations and to motivate why experimentalists have begun to suggest a new origin for rhythms driving Parkinson's, the hyperdirect pathway. An activity model of individual STN cells was built and a finite element grid for voltages was used to apply stimulation. Measured local field potentials from the activity model of coupled neurons without DBS and compared it to patient data to constrain the parameter space. Using independent validation data the speakers have shown early agreement between the model and the validation data. Patient-specific DBS model that focuses on the hyperdirect pathway that has been experimentally studied was described to be one of the next modeling steps. In the future, the speaker talked about how biophysical models of network origin of the pathological cortical activity can help inform disease suppression. Additionally, an outline was given on how closed-loop systems modeling adaptive DBS could also implemented.

Model-free approaches to controlling neuronal circuits
ShiNung Ching (Washington University)
Can we ‘’play” a spike pattern into a specific population of neurons? The goal of Dr. Ching’s work is to go from a perturbative framework to a more precise controlled framework where by tuning and designing stimulations, asynchronous, selective and timed patterns of spiking in brain activity at neuronal scale can be induced. Control theory can help to obviate this issue by optimizing extrinsic inputs for maximizing activity-based objective functions. However, the deployment of classical control methods at neural level is challenging. In this talk, Dr. Ching discussed approaches that do not require an explicit mathematical model for the circuit to be controlled in three aspects: first, he analyzed the problem at a basic mathematical level and looked at the fundamental limits of forced spiking in small populations; then, he relaxed the problem to optimize spiking patterns approximately; and finally, he added back limitations and showed how to control networks with networks to obtain selective and timed spiking in a model-free setting.

Control of Discrete and Rhythmic Motor Skills - A Task-Dynamic Approach
Dagmar Sternad (Northeastern University)
While everyday actions flexibly combine rhythmic and discrete movement elements, motor neuroscience research has largely studied these movement types in isolation, developing separate accounts for these two movement forms. In this talk, Dr. Sternad proposed that rhythmic and discrete behaviors are two dynamic primitives constituting more complex actions and supported her claim by a series of brain-imaging, behavioral and modeling studies. Her research analyzes how task dynamics constrain and enable actions and their improvement with practice. In her analysis pipeline, she starts with a mechanical model of the task and render it in a virtual environment with a fully

known solution space. Then, based on mathematical analyses of the modeled task, she investigates how humans develop solutions to meet complex task demands. Key concepts in her analysis are variability, stability, and predictability. Using three model tasks, throwing a ball, rhythmic bouncing of a ball, and transporting a cup of coffee, Dr. Sternad showed that humans develop skill by: 1) finding error-tolerant strategies and channeling noise into task-irrelevant dimensions, 2) exploiting solutions with dynamic stability, 3) optimizing predictability of object dynamics. These findings are the basis for developing propositions about the controller: complex actions are generated with dynamic primitives, modules that overcome substantial delays and noise in the neuro-mechanical system. Extending from these experimental platforms her group have developed interventions that assess or help restore functional behavior in neurological patients.

Control of Weakly (and Not So Weakly) Perturbed Neural Oscillatory
Dan Wilson (University of Pittsburgh)
While high-frequency deep brain stimulation (DBS) is a decades old treatment for alleviating the motor symptoms of Parkinson's disease, its mechanisms are not well understood. Some experimental evidence suggest that DBS works by making neurons fire more regularly, while other seemingly contradictory evidence suggests that DBS works by making neural firing patterns less synchronized. In his lecture, Dr. Wilson presented theoretical and numerical results that suggest that these two mechanisms are not mutually exclusive. Specifically, in a noisy group of phase oscillators, high frequency perturbations can separate the population into multiple clusters, each with a nearly identical proportion of the overall population. Exploitation of this phenomenon could lead to better DBS protocols.

Organization and Control of Hippocampal Circuits
Ivan Soltesz (Stanford University)
In this talk, Dr. Soltesz talked about how we can understand hippocampal cortical functions in general using various approaches. Distinct inhibitory cell types deliver GABA to specific spatial domains of principal cells at particular times during behaviorally relevant network oscillations. Using experimental data from the hippocampus of awake mice, Dr. Soltesz showed that emerging meta rules exist for chronocircuit organization and regardless of frequencies, there is always temporal ordering in interneuronal discharges between very different types of cells. By focusing on epilepsy, Dr. Soltesz then addressed the question of how to control abnormal activity in hippocampal circuits, for which a closed-loop system design is required. Finally, to study network function and dysfunction, Dr. Soltesz and his collaborators built data-driven full-scale models of the hippocampal circuits which show good match with experiments and provide new insights into circuit dynamics such as the role for the slow GABAA from neurogliaform cells.

Stochastic Optimal Control and Sensory focussing
Andre Longtin (University of Ottawa)
The talk was divided into two parts: the first part covered stochastic optimal control of neural firing times and the second covered the control neural focus. In the first part, closed and open loop control frameworks were considered and the neural firing dynamics were modeled with a noisy leaky integrate and fire model, or an Ornstein-Uhlenbeck process. If only the spike timing was known, then open loop control was used. If there was voltage mesaurements then closed loop control was used and the goal was to apply a control to achieve a specified threshold crossing time. Closed loop control was also applied to the more sophisticated Morris-Lecar neural model after using results from the literature to convert it to a Ornstain-Uhlenbeck. In the second part, the

speaker focused on how the electrosensory system interprets with signals from the environment. The sight of fish was the application here and experiments found that they can best track object that were about 1.3cm from their skin. Applying Fisher information theory to the Poisson process used for modeling this same distance was of 1.3cm was found to be optimal.

FRIDAY, SEPTEMBER 15, 2017

Adaptive Locomotor Behavior: Neural Mechanisms Underlying Coordination of Motor Activity in a Six-Legged Biological Walking System

Ansgar Büschges (Institute for Zoology)

A main function of animals' nervous systems is the generation of motor behaviors. Dr. Buschges is interested in unravelling the neural basis of animal motor flexibility from relatively easy locomotor behaviors such as swimming, flying and crawling, to challenging behaviors such as climbing, quadruped walking and biped walking. By presenting recent findings on a six-legged biological walking system, Dr. Buschges illustrated how can the neuronal network allow for adaptive locomotor behaviors regardless of perturbation such as generating turns during locomotion to avoid an obstacle; this arises from side specificity of both descending drive to local CPGs and processing of movement and load signals. He also addressed the question of animals coping with unpredictable terrain and showed this is assisted by local command-like interneurons, the action of which is regulated by local feedback from the leg. Finally, Dr. Buschges discussed how these neuronal networks interact with each other to generate proper coordination for locomotion, e.g., interleg coordination of a walking animal.

How do we manage it? The paradox of human performance

Neville Hogan (Massachusetts Institute of Technology)

Despite slow actuators, complexity (600+ muscles), slow communication neurons and long feedback loop delays, human dexterity and agility significantly out-perform contemporary robots. How is this possible? Delays and slow response impair reactive control, while agility despite delays implies predictive control based on "internal models", e.g., in the cerebellum. However, what form do these internal models take in biology?

Modeling using differential equations is challenging even for modern super-computers. In this talk, Dr. Hogan talked about one possible alternative: internal model based on dynamic primitive that can be any attractor in a dynamical system. Evoking dynamic primitives may require minimal central control yet achieve high performance because each primitive is highly dynamic behavior.

In addition to using observations in stoke patients to show biological evidence for this proposal, Dr. Hogan reviewed a surprising limitation arising from control via dynamic primitives, that is, moving slowly is hard for humans. A special class of dynamic primitives, neuro-muscular mechanical impedance, is the key to controlling physical interaction. Dr. Hogan argued that both motion primitives reflecting motor planning in a domain of information processing and impedance primitives dictating physically reactive behavior in a domain of energy processing need to be combined by a nonlinear generalization of the classical equivalent electric circuit. In the end, Dr. Hogan suggested that nonlinear equivalent networks provided a general basis for the internal models required for high-performance interactive control and especially physical human-robot interaction.

Using Randomness in Locomotion

John Guckenheimer (Cornell University)
Animal locomotion is incredibly complex system involving interactions between the nervous system, the body and the environment. To understand the stability of motor control, in this talk, Dr. Guckenheimer put together theory including dynamical systems with stable periodic orbits, control theory for periodic orbits and stochastic processes perturbing periodic robust, experimental data from people running on treadmills, and models that involve mechanical mechanisms, central pattern generators and data driven dynamics systems.

For studying principles of locomotion control in order to maintain stability in running, Dr. Guckenheimer combined together a mechanical template: spring loaded inverted pendulum (SLIP), and a more abstract template: stochastic perturbation of hybrid stable limit cycle. He then talked about the computation of SLIP parameters, the SLIP control that comes from controlling the stiffness of the spring and pointing the leg at desired directions during the liftoff phase, as well as using principal components analysis of full-state controller to obtain reduced controllers which can give similar predictions. Furthermore, Dr. Guckenheimer discussed the estimation of the Floquet multipliers which characterize local stability properties of a periodic orbit in stochastic differential equation. He showed that uncontrolled SLIP is unstable, therefore, control is needed step by step in order for animals to maintain stability.

Autumn Workshop 2 - Control of Cellular and Molecular Systems (October 2-6, 2017)

Organizers: Hana El Samad (University of California, San Francisco), German Enciso (University of California, Irvine), Pablo Iglesias (Johns Hopkins University), Mustafa Khammash (ETH Zurich)

Report by: Veronica Ciocanel, Punit Gandhi, and Yangyang Wang

MONDAY, OCTOBER 2, 2017

Antithetic Integral Feedback: A New Motif for Perfect Adaptation
Mustafa Khammash (ETH Zurich)
The ability to adapt to stimuli is a defining feature of many biological systems and critical to maintaining homeostasis. Robust perfect adaptation in biology can be realized through the use of integral feedback control. In this talk, Dr. Khammash presented the underlying theory and first implementation of an integral feedback control system that can achieve perfect adaptation in a living cell. The controller is based on a new motif for robust perfect adaptation called antithetic integral feedback. This motif exploits stochastic noise, allowing it to achieve precise regulation in a scenario where similar deterministic regulation fails. Specifically, antithetic integral feedback preserves the stability of the overall network, steers the population of any regulated species to a desired set point, and adapts perfectly. In addition to showing implementations of antithetic integral feedback controller on E. Coli and mammalian cells, Dr. Khammash also discussed how to resolve practical implementation issues such as the degradation and dilution terms leading to an imperfect adaptation, the saturation that will lead to the opening of the loop and the possible variance increase.

Engineering Robust Molecular Feedback Controllers via Ultrasensitive Modules
Elisa Franco (University of California, Riverside)

Given a bimolecular system, how do you build a bimolecular controller? In this talk, Dr. Franco described a molecular reaction network that can be used to achieve robust closed loop control in synthetic biology. The network is based on the "brink controller" motif which results from combining sequestration and zeroth-order ultrasensitive responses. In addition to describing the properties of this brink controller motif and discussing the challenges of simultaneous negative and positive action on the system to be controlled, Dr. Franco also showed how to implement the brink motif using aptamers and viral RNA polymerases. In the end, Dr. Franco presented an ongoing collaborative project on building proportional-integral-derivative controllers using RNA riboregulators and the CRISPR/Cas system.

Cancer Modeling: Optimal Therapy Scheduling Based on a Pair of Collaterally Sensitive Drugs
Nara Yoon (Cleveland Clinic Foundation)
Drug resistance is one of the main hurdles in cancer therapy. In this presentation, Dr. Yoon talked about their recent studies on how to minimize drug resistance by choosing the right schedule of a pair of collaterally sensitive drugs. The model developed is a piecewise continuous ODE on the population of two distinct cancer cell groups resistant to each drug, respectively. Regarding this model, Dr. Yoon first introduced the analysis and numerical derivation of the optimal drug-switch timing, as well as the relationship between population makeup and drug effects. There are certain population makeup levels at which the two drugs have the same effects. Next, Dr. Yoon talked about a stochastic simulation algorithm extended from their model which produces consistent results to the deterministic ODE system, the distribution of extinction times for the classes of solutions are also presented. Last, Dr. Yoon introduced an application of the model extended to a one dimensional PDE system to simulate the cell population over space and time in blood vessel.

Modeling and Design of Feedback Circuits in Biology
Antonis Papachristodoulou (University of Oxford)
Dr. Papachristodoulou talked about feedback control systems, which are found extensively in many natural and technological systems. He started with the motivating examples of biological processes such as bacterial chemotaxis in E. coli and negative autoregulation in genetic circuits, which use feedback to regulate key processes. Despite the prevalence of feedback in natural systems, its design and implementation in a Synthetic Biology context is much harder.

Dr. Papachristodoulou provided examples of how his lab has implemented negative feedback design in three different biological systems. In the first one, they designed a synthetic recombinase-based feedback loop and used a differential equations model for gene expression. The results with this closed feedback loop showed lower levels of noise and therefore robust expression. In the second example, they used small RNAs to post-transcriptionally regulate gene expression through interaction with messenger RNA (mRNA) using two types of circuits. They observed that they could regulate output without introducing too much noise. The third example involved the introduction of negative feedback in a two-component ligand-receptor signalling system through a controllable phosphatase. This created a "writer-eraser" structure which led to tunable regions. In closing, he mentioned that tuning feedback for particular applications maintains challenges which may be addressed with, extensive modeling of the biochemical reactions, by using synthetic biology concepts, and by performing simulations and implementation. Challenges remain since synthetic constructs may not be robust to uncertainties and disturbances.

Multiple Metabolic Signals Establish a Deterministic Cell Fate Decision

Nihal Ezgi Temamogullari (University of Texas Southwestern Medical Center)
Dr. Temamogullari talked about single cell resolution and the observation that isogenic cells exposed to the same environmental cues will choose between different fates. In particular, she addressed questions such as predicting the cell fate of individual cells, and how far before commitment one can predict this fate. To understand how deterministic this process is, they developed an experimental-theoretical framework to follow various signals that cells are integrating continuously throughout the course of decision-making. As a model system, they used budding yeast meiosis, where upon nutrient limitation, cells either commit to meiosis (and sporulate) or become quiescent. Using fluorescent traces of two proteins in this system, they can observe cell birth, mitotic arrest, and meiosis events, and can predict cell fate with high accuracy based on the average cell size. To look beyond cell size and instead focus on the regulating processes, they coupled microfluidics and time-lapse microscopy, which allowed imaging up to 6 endogeneously tagged fluorophores in single cells from exposure to differentiation signal to the realization of a particular fate. To combine these high dimensional observations into fate probabilities, they used statistical evidence that translated these measurements into fate probabilities. In this way, they could follow the 'predisposition' of each cell towards a certain cell fate over the entire decision-making process. With this framework, they followed the metabolic markers of single cells and were able to predict cell fates with very high accuracy up to four hours before the commitment point. They also concluded that the "decision point" corresponding to the fate the cells would choose under nutrient limitation was typically before birth for most cells.

TUESDAY OCTOBER 3, 2017

Multi-Objective and Multi-Scale Design of Synthetic Gene Circuits
Jeorg Stelling (ETH Zurich)
Dr. Stelling described strategies for designing synthetic gene circuits that can operate in natural systems such as cells or organisms where resources are limited by the surrounding environment and cross-talk must be accounted for. His approach relies on Bayesian methods that identifies circuit topologies whose behavior is robust to variations in parameters. By iteratively constructing a heirarchy of models of increasing complexity from the top down and applying topological filtering, the strategy enables design that reliably assess trade-offs between performance, robustness, and experimental feasibility. Dr. Stelling then discussed a biomedical application of synthetic gene circuit design for in vivo closed loop control for the treatment of type 1 and 2 diabetes. He and his collaborators achieved glucose responsiveness by a synthetic circuit that couples glycolysis-mediated calcium entry to an excitation-transcription system controlling therapeutic transgene expression.

Balancing a genetic toggle switch using real-time control and periodic stimulation
Gregory Batt (InBio, Inria Saclay - Ile-de-France and Institut Pasteur)
Dr. Batt demonstrated the ability to control single yeast cells to remain in an undecided state for an extended period of time and provided evidence that the method can be extended to controlling populations of cells. This was achieved via in silico feedback, by controlling a multistable gene regulatory network that plays a critical role in cell differentiation and decision-making. The idea has been benchmarked in a genetic toggle switch where control-induced periodic forcing maintains the system near an unstable equilibrium. The experimental results are consistent with simulations based on a model of the system. The results pave the way for the control of more complex cell

decision-making systems at both the single cell and population levels, with fast fundamental and biotechnological applications.

Using Mathematical Modeling to Understand the Role of Diacylglycerol (DAG) as a Second Messenger
Mary Ann Horn (Case Western Reserve University)
Diacylglycerol (DAG) regulates a variety of cellular processes and the breakdown of the signaling pathway that involves DAG contributes to a variety of diseases, including cancer. Dr. Horn and her collaborators have developed an ODE model of the Uridine Diphosphate (UDP) signaling pathway in RAW 264.7 macrophages that can predict the responses of multiple species of DAG as well as the responses of IP3, Ca2+, receptor dynamics, G-protein activation, and PIP2 hydrolysis. Global existence, uniqueness, positivity, and boundedness of solutions has been obtained for a simplified version of the model. Parameter estimation for the full model was carried out using laboratory data, and sensitivity analysis was used to determine which model parameters are most responsible for the model output uncertainty.

Optogenetics for intracellular codebreaking: how signaling stimuli is interpreted to control gene expression and cell behavior
Jared Toettcher (Princeton University)
Dr. Toettcher described recent work to develop light-sensitive proteins that control basic signaling processes in mammalian cells and Drosophila embryos that can be used to experimentally probe cell signaling networks across these model systems. Using optogenetic control he was able to dissect how Erk signaling controls gene expression and cell fate in fly embryos. He also carried out experiments to study how cells can maintain a polarized state after a transient stimulation and developed a simple model for spatiotemporal aggregation consistent with his experimental results.

Bacterial dynamics in time and space
Lingchong You (Duke University)
Dr. You argued that addressing the antibiotic crisis in which microbial resistance is beginning to emerge faster than new drugs can be developed requires two complementary strategies. First to continue to develop novel drugs and therapeutic methods to combat bacterial infections. Secondly, it is critical to develop effective antibiotic treatment protocols that can extend the efficacy and usability of existing antibiotics. This requires an intermediate level of mechanistic understanding of both the short-term and long-term bacterial dynamics in response to antibiotic treatment. One example discussed by Dr. You is the persistence of the costly resistance gene in bacteria even in the absence of antibiotics within the environment because of horizontal gene transfer. Indeed, experiments show that targeting conjugation to prevent horizontal gene transfer successfully mediated drug resistance.

WEDNESDAY OCTOBER 4, 2017

Dynamics Response Phenotypes in Systems Biology: Scale-Invariance and Monotone I/O Systems
Eduardo Sontag (Rutgers University at New Brunswick)

Dr. Sontag focused in this talk on dynamical phenotypes in cell signaling and metabolic pathways that may be critical to true phenotypes (such as cell cycle arrest and senescence).

“Dynamic phenotypes” are characterized by input/output responses to external inputs, and the examples in this talk included fold-change detection and monotone architectures.
Dr. Sontag began by discussing an ubiquitous property of sensory systems, "adaptation", which mean that a step increase in stimulus triggers an initial change in a biochemical or physiological response, followed by a more gradual relaxation toward a basal, pre-stimulus level (perfect adaptation corresponds to returning to the pre-stimulus value). Adaptation helps maintain essential variables within acceptable bounds and allows organisms to readjust themselves to an optimum and non-saturating sensitivity range when faced with a prolonged change in their environment. He then mentioned that recent observations in some adapting systems, such as the wnt signal transduction mechanisms in Xenopus, show the additional feature of scale invariance or "fold change detection". This means that the initial, transient behavior remains approximately the same when the background signal level is scaled to different levels.

The talk introduced the theoretical framework of feedforward loops, which are an ubiquitous motif in biological networks, and specifically incoherent feedforward loops (IFFL), which can adapt and detect changes. This framework lead to a general theorem characterizing scale invariant behavior by equivariant actions on sets of vector fields that satisfy appropriate Lie-algebraic nondegeneracy conditions. The theorem allowed to make experimentally testable predictions, and Dr. Sontag discussed the validation of these predictions using genetically engineered bacteria and microfluidic devices in chemotaxis, as well their use as a "dynamical phenotype" to show that certain existing models and parameters cannot be validated. Dr. Sontag concluded with some remarks about how to distinguish between IFFL and negative feedback loops, suggesting that testing with periodic inputs may be one possible direction.

Spatial Patterns of Gene Expression in Multicellular Ensembles
Murat Arcak (University of California, Berkeley)
Dr. Arcak discussed the importance of predicting and controlling gene expression patterns in multicellular ensembles for developmental biology and the challenge of this control in synthetic biology. He suggested that in certain systems (such as fish pigmentation patterns), breaking symmetry spatially may require mechanisms such as diffusion-driven patterning and lateral inhibition. He described a unified dynamical systems modeling paradigm for patterns in gene expression that can account for diffusion through a Laplacian matrix or for lateral inhibition through an adjacency matrix, and explained that the unsteady steady state leads to spontaneous patterning.

Dr. Arcak also focused on using this paradigm to investigate model sensitivity, by representing the external input and output in a spatial basis and analyzing the sensitivity of each spatial node to spatially varying external output. With the help of these dynamical models, he highlighted the key structural properties that are necessary for patterning and presented novel synthetic gene networks built upon these models.

Controlling Biological Oscillators
Jeff Moehlis (University of California, Santa Barbara)
How to control complex and high dimensional systems of physical, technological and biological interest? Many of these systems can be viewed as nonlinear oscillators - dynamical systems with stable periodic solutions, the control of which will then be much simpler. Examples from biology include pacemaker cells in the heart, the firing of action potentials in neurons, and circadian rhythms. In this talk, Dr. Moehlis talked about controlling individual oscillators as well as controlling

population of oscillators, by developing an optimal control algorithm to change the phase of a periodic orbit using a minimum energy input. However, the control algorithm based on standard phase reduction fails when a large change in time period is required or when the nontrivial Floquet multiplier of the periodic orbit is close to one. For the technique to be effective in such cases, the transversal distance to the uncontrolled periodic trajectory will also need to be minimized. Dr. Moehlis therefore used a two-dimensional augmented phase reduction technique based on both isochrons and isostables. Inspired by deep brain stimulation treatment of Parkinson's disease, in the second half of the talk, Dr. Moehlis talked about desynchronizing neural populations using the control algorithm they developed, for example, by maximizing the Lyapunov exponent associated with their phase dynamics and through optimal phase resetting. Dr. Moehlis also introduced an alternative control objective for desynchronization: find electrical stimulus which leads to clustering of neural activity using minimal power.

Design of de novo biomolecular feedbacks for improved performance and robustness in living cells

Guy-Bart Stan (Imperial College London)

In this talk, Dr. Stan gave an overview on developing foundational forward engineering methods to mathematically model, control and experimentally implement synthetic gene circuits and cellular systems that aim at increasing the robustness, performance and genetic stability of engineered cells.

Overall, Dr. Stan talked three projects: 1) Heterologous gene expression can be a significant burden for cells. Dr. Stan described quantification of cellular capacity and identification of construct designs with reduced burden that predictably outperformed less efficient designs, despite having equivalent output. 2) Cells use feedback regulation to ensure robust growth despite fluctuating demands on resources and different environmental conditions. Yet the expression of foreign proteins from engineered constructs is an unnatural burden on resources that cells are not adapted for. Dr. Stan and his collaborators therefore built a CRISPR/dCas9-based feedback regulation system that automatically adjusts synthetic construct expression in response to burden. He showed that cells equipped with this general-use controller maintain capacity for native gene expression to ensure robust growth and as such outperform unregulated cells at protein yields in batch production. 3) Engineering robust and tunable genetic clocks is a topic of current interest in systems and synthetic biology with wide applications in biotechnology. Recently the dual-feedback oscillators was demonstrated to be robust and tunable, to some extent, by the use of chemical inducers. Yet no engineered genetic oscillator currently allows for the independent modulation of amplitude and period. Dr. Stan demonstrated computationally how recent advances in tunable synthetic degradation can be used to decouple the frequency and amplitude modulation in synthetic genetic oscillators. The ability of tuning period and amplitude independently allows us to infer multiple inputs from a single output biosensor because period values and amplitude values change independently from each other.

Synthetic biology approaches to suppression of antibiotic resistance: toward model-based design

Brian Ingalls (University of Waterloo)

Dr. Ingalls talked about antibiotic-resistant pathogens, which present an increasing global health concern. In particular, his group is investigating synthetic biology-based strategies for suppression of resistance in environmental bacterial populations. Their approach involves the delivery of engineered mobile genetic elements to target populations.

The first model Dr. Ingalls discussed was on plasmid delivery dynamics, with adjustments such as distinct kinetics for donors and recipients as well as nutrient limitation. Using the Akaike Information Criterion, they reduced a large comprehensive model to a reduced formulation with insights that agree with experiments. The second model he discussed was a 2-species Lotka-Volterra model with additional interactions used for the comparison of different conjugation strategies. Here sensitivity analysis was carried out using Sobol's method. In the third example, Dr. Ingalls discussed displacement of resistance plasmids by unilateral incompatibility. He presented ideas for using Markov chain population models as well as preliminary experiments from the lab. He explained that these models of the dynamics of this system, at both the genetic and population level, will be used for model-based design of potential implementations.

Set point control, excitable systems and cell migration
Pablo Iglesias (Johns Hopkins University)
Dr. Iglesias talked about recent experimental evidence that the migration of cells is regulated by a network displaying excitable behavior. Stochastically generated firings of this excitable system can generate random actin-filled protrusions that propel cells. He focused on cell migration in chemotaxis, and in particular amoeboid mobility through actin protrusions, and asked the question of what external cues lead to creation of these protrusions.

Using TIRF microscopy, his lab has noticed actin waves of polymerization and studied wave propagation using a Fitz-Hugh Nagumo activator-inhibitor model for the excitable network. By applying perturbations to a stochastic reaction-diffusion model, they also observed that they can modify the set point of the excitable system and observe different migratory patterns both theoretically and experimentally in the amoeboid. For example, the model could predict oscillatory behavior as well as bifurcations. Dr. Iglesias concluded that by altering the threshold of the excitable system in a spatially-dependent manner, external stimuli can bias this stochastic activity to direct cellular motion.

THURSDAY OCTOBER 5, 2017

Absolute Robustness and Output Stabilization in Stochastic Chemical Reaction Networks
German Enciso (University of California, Irvine)
Absolute robustness is a structural property ensuring that the steady state output of a chemical reaction network is unchanged as a function of total protein concentrations. Dr. Enciso discussed the generalization of this property to stochastic networks where robustness is the insensitivity of the network output to the presence of noise. He provides a theorem that generalizes the result for deterministic systems with deficiency of one to stochastic systems. The approach is to reduce the model by variable freezing where some variables as constant are taken as constant. In principle ensuring absolute robustness requires global knowledge of the network in order to calculate network deficiency. However Dr. Enciso also discusses the stabilization of a given network with the addition of a deficiency one module.

Applications of external control of gene expression in yeast and mammalian cells
Diego di Bernardo (Universit'a di Napoli "Federico II")
Dr. di Bernardo's discussed the use of model predictive control on gene expressions from chemically inducible promoters in two cases: yeast cells and mammalian cells. Overexpression of alpha-synuclein in yeast cells has been shown to lead to aggregation which is toxic. Dr. di Bernardo was

able to use external control feedback to show aggregation occurs at a specific threshold of alpha-synuclein which is lower for mutant versus wild types. By developing a microfluidic device that relies on diffusion to send changes from controller, Dr. di Bernardo also demonstrated control of gene expression in mammalian cells thus opening up a plethora of applications in human cells.

Build to Perturb, Perturb to Understand
Hana El Samad (University of California, San Francisco)
Dr. El Samad discussed several examples where synthetic biology tools interface with endogenous biological systems and perturbations of the systems using these tools reveal organization and function. She provided the example of the insertion of two different controls via synthetic transcription factors to untangle the connectivity within a given pathway. Dr. El Samad then discussed several other tools to perturb and control cells with high precision including two complimentary optogenetic tools called LOVTRAP and LANS that together can reliably trap/release and precisely guide molecules. She concluded by posing the question: What can we do with all of these tools?

Control in single cells
Johan Paulsson (Harvard University)
Dr. Paulsson discussed the idea that reactions that involve small numbers of molecules generate spontaneous fluctuations that then enslave all dependent processes. He focused on the concept that stochastic noise in low-number molecules or cells may not simply lead to small levels of "noise" but rather may be driving and randomizing processes such as developmental pathways or cell cycle control.

The first example he gave was the idea that some cells may fail to repair DNA damage because they may have fewer than average repair molecules. Using *E. coli* as the model organism, they showed that only some cells turn on repair expression after damage, and that stochastic production of a single protein may determine the fate of the cell. The second example was that of cell fate decision in *B. subtilis*, where cells move around in a memoryless manner and may be in motile or chained states. Dr. Paulsson showed that simplifying a complex system of control loops to only a few simple reactions still captured most of the observed behavior, and confirmed this with experiments in *E. coli* as well. Finally, his last example involved the first synthetic oscillator (the repressilator) modified using the stochastic chemistry of single cells. By removing some features, they were able to achieve more regular and robust oscillations.

Elucidating network design principles of microbial consortia for controlling ecological states
Ophelia Venturelli (University of Wisconsin)
Dr. Venturelli spoke about microbial communities, which are coupled networks of diverse organisms operating on multiple time and spatial scales that occupy nearly every environment on Earth. She is interested in gaining a detailed and quantitative understanding of microbial communities through predictive modeling of community dynamics and studying community-level functions through microscopic interactions. Forecasting the dynamic responses of these communities would enable the design of targeted interventions using synthetic biology to shift communities to desired states.

Dr. Venturelli described a generalizable model-guided approach to reverse engineer microbial interactions that shape the assembly of a human gut microbiome synthetic ecology. Using time-series measurements of population dynamics and a generalized Lotka-Volterra model, they built a

predictive model of community dynamics and identified different types of dynamics such as dominance, stable coexistence, and history-dependence. This allowed to determine the ecological roles of various species as well as pinpointed influential and ecologically responsive species that were significantly modulated by microbial inter-relationships. Her works shows that pairwise interactions are major drivers of multi-species community assembly as opposed to higher-order interactions, as they can explain the majority of the observed dynamics. In the future, she is interested in using these results to design synthetic circuits and microbiomes for feedback control with the goal of restoring healthy microbiome states.

FRIDAY OCTOBER 6, 2017

Synthetic Biology: Engineering Sophisticated Gene Regulation for Therapeutic Systems
Ron Weiss (Princeton University)
Synthetic biology is revolutionizing how we conceptualize and approach the engineering of biological systems. Recent advances in the field are allowing us to expand beyond the construction and analysis of small gene networks towards the implementation of complex multicellular systems with a variety of applications.

Example synthetic biology application areas drives the outline of the talk: 1) Dr. Weiss discussed experimental results with synthetic biology building blocks for intracellular sensing, processing and actuation in mammalian cells. He showed that in order to create and maintain large scale spatially defined functional tissues using genetic program, precise spatially, temporarily, cell-type specific control is needed. Possible applications of this lie on drug development, disease models as well as organ translation. 2) Switching to genetically encoded therapeutic programs for cancer therapy, Dr. Weiss presented a genetic circuit that can detect and destroy specific cancer cells based on the presence or absence or specific biomarkers in the cell. Specifically, the bio-program consists of five steps: initial infection, selective spread, initial cancer cell death, recruit immune system and finally immune system assisted tumor eradication. 3) Finally, Dr. Weiss discussed creating regulatory circuits based strictly and purely on protein-protein interactions. These circuits can modulate existing pathways and are fast networks with potentially lower operation, thereby creating opportunities for new synthetic biology capabilities and applications.

Competition for Cellular Resources in Genetic Circuits and its Mitigation Through Decentralized Feedback Control
Domitilla Del Vecchio (Massachusetts Institute of Technology)
Designing sophisticated systems that function as intended is challenged by the fact that functional modules are context-dependent, wherein the input/output behavior of a system depends on the context. For example, load between modules is one source of context dependence. Modules also apply a load to the cellular system such that genes, modules and systems all compete with each other for a limited supply of cellular resources. This competition for resources, as a common problem in engineering systems, creates subtle couplings among circuits' components, which can dramatically change the circuits' intended behavior. Including both analysis and designing, Dr. Del Vecchio described a design-oriented predictive model of competition effects and a control theoretic framework to mitigate these effects. Specifically, retroactivity between modules is one source of context dependence, which can be fixed by designing insulation devices. Modules also apply retroactivity to the cellular system which creates subtle couplings. Dr. Del Vecchio talked about how to uncover and model hidden interactions due to sharing finite resources in gene circuits and

proposed decentralized feedback controllers to fix this. Their results enable resource-aware rational design of genetic circuits and set the basis for future genetic circuits that work robustly despite resource limitations.

Autumn Workshop 3 - Control of Disease: Personalized Medicine Across Heterogeneous Populations
(October 30-November 3, 2017)

Organizers: B. Wayne Bequette (Rensselaer Polytechnic Institute), Gilles Clermont (University of Pittsburgh), Franz Kappel (University of Graz), Mette Olufsen (North Carolina State University)

Report by: Veronica Ciocanel, Reginald McGee, Farrah Sadre-Marandi

MONDAY, OCTOBER 30, 2017

Challenges for Mathematical Modelling in the Era of Personalized Medicine
Franz Kappel (University of Graz)
The speaker presented a mathematical model for erythropoiesis, red blood cell development. He began with a motivation for the structure of the model which was multicompartmental and contained dynamics for cell concentrations within both the bone marrow and in the plasma. Due to wide variability in the data, the speaker stressed the need for model attributes such as cell age and hemoglobin concentration would have to be included in their model if would be fit to individual patient data. The model included both ordinary and partial differential equations with a total of thirty parameters. Dr. Kappel conducted sensitivity analysis to separate out five parameters that could be individualized for each patient. The speaker presented two examples of strong quantitative agreement between the model and patient data. To conclude, the speaker motivated the need for maximum likelihood estimates and filtering methods in parameter estimation as models become increasingly more complex.

Managing Blood Sugar and Kidney Health
Anita Layton (Duke University)
Dr. Layton began her talk with an overview of renal physiology to motivate the multiscale model of kidney dynamics that would be considered. The aim of this work was to make predictions on how glucose levels in diabetic patients can be better managed. The speaker was interested in developing a drug to inhibit of the sodium-glucose co-transporter (SGLT2) found specifically in certain regions of the kidney, but not in other areas of the body. A concern beyond non-specific binding of the inhibitor was whether SGLT2 inhibition has an adverse effect on downstream segments of the kidney's proximal tubule. To investigated this concern, an epithelial-based model of water and solute transport through the kidney nephron was used to consider the case of acute and chronic SLGT2 inhibition. The model found that SGLT2 inhibition substantially reduced the proximal tubule glucose and sodium reabsorption, but may overload downstream segments. A limitation of the model was that the data used in baseline results were from healthy individuals. Thus, the speaker considered data in the case of a a diseased kidney, particularly in the case of nephrectomy when there is a strong reduction in the number of nephrons. The diseased model predicts that fewer nephrons enhances diuretic, natriuretic, glucosuric, and kaliuretic effects and these effects may contribute to the reduction in blood pressure and heart failure observed in diabetic patients receiving SGLT2 inhibitors.

Diabetes Treatment: One Size does not Fit All
Eda Cengiz (Yale School of Medicine)
To motivate the need for improved closed loop systems to combat diabetes, Dr. Cengiz began her talk with a review of the disease and the current state of treatment. Previously, plans of treatment revolved around metrics such as weight that did not consider individual biochemistry and metabolism. In certain trials, it was found that that 70-80% of patients with Type 1 Diabetes (T1D) were being poorly controlled. Closed loop systems have been helpful in helping diabetic patients providing customized insulin treatment, but there have been obstacles with technology like insulin dosing errors and delivery lags. The introduction of the continuous glucose monitor has resolved some of these issues, eased patient burden, and provides a way for continuous glucose dynamics to be collected if patients donated their data to the Type 1 Diabetes Exchange Database. In the future this continuous-time data can be mined to make better glucose management algorithms for devices. Though diabetes technology is improving care by automating process there is a need for ultra-fast acting insulins to improve the rate at which blood glucose can be managed. This is due to the inherent heterogeneity in absorption amongst patients, fast acting insulins will help patients who absorb normal insulin at a slower rate than the mean delivery lag.

Automated Insulin Delivery: An Overview of Models and Algorithms
B. Wayne Bequette (Rensselaer Polytechnic Institute)
The speaker began with a motivating example of an asymmetry in blood glucose control and how fitting treatments to a mean can lead to long term issues. To motivate the need for more continuous monitoring of glucose levels the speaker went through examples on how insulin needs can drastically exceed basal insulin and instantaneous delivery of insulin can be impractical. The aim of the work here was to move towards a fully closed loop system where blood glucose can be managed with reasonable doses without the user having to specify when meals will occur. Both ease of use for the patient and human error inputting accurate information into their artificial pancreas drives the need for adding meal prediction to the device's control algorithm. Dr. Bequette gave an overview of models that have been used for artificial pancreas systems and ultimately decided on a eleven state compartmental model with a proportional–integral–derivative controller. Using a Kalman filter framework to make predictions, the speaker's group conducted trials on when to suspend insulin pump activity when your glucose levels enter a low-glucose regime. Finally, the speaker showed how his group was using model predictive control with probability distributions on the mean blood glucose levels to move towards a fully closed loop system that can manage blood glucose without patient input, for instance during sleep.

Probabilistic Aspects of the Artificial Pancreas and Fully Closed Loop control
Faye Cameron (Rensselaer Polytechnic Institute)
This talk explained how controllers are used by artificial pancreas algorithms in blood glucose management and showed the need for robustness to uncertainty like missed or unexpected meals. To illustrate the type of uncertainties that are present in these controllers the speaker gave a review of the asymmetries that are present in the blood glucose management problem: an asymmetric cost function that needs to be minimized, an asymmetric controller represented by insulin, and asymmetric disturbances represented by meals. Handling this uncertainty required that the adapting the controller was divided into considering the both control law and the predictor. Adapting the control law required the development of a distribution on the level of glucose over time and then insulin was injected to minimize the future cost or risk function. Adapting the

predictor required more consideration of how to detect and anticipate disturbances like meals. Incorporating meal detection used multiple models weighted by priors that were determined using data from the American Time Use Survey Eating & Health (EH) module. The speaker suggested that moving forward more sensors would be needed to track different activities like sleep, exercise, and eating and build profiles patients to advance towards fully closed loop control.

TUESDAY, OCTOBER 31, 2017

Dynamical Systems Modeling to Identify Cohorts of Problem Drinkers with Similar Mechanisms of Behavior Change

H.T. Banks (North Carolina State University)

The speaker began with formal definitions for problem drinking from psychology and numerical ranges to classify that drinking category. This collaboration with psychologists seeks to use an iterative modeling approach to build a mathematical model to understand problem drinker's choices. The model seeks to track variables like overall consumption, guilt or norm violation, confidence in avoiding heavy drinking, and commitment to avoid heavy drinking. A challenge was that the data used could be incomplete if the participant couldn't remember the number of drinks they had and there was a possibility of the data being incorrect if the participant underreported the number of drinks they had or lied about their commitment or confidence. Moreover, the data had a finite number of possibilities since it was often collected as a survey response and the models considered here are continuous in time. The initial model was constructed with a top-down approach where the speaker proposed mechanisms for the variable dynamics. The model and data agreed qualitatively and provided strong support for mathematical modeling to describe dynamic drinking behavior, particularly since typical statistical methodologies did not lead to a better understanding. The revised model used a bottom up approach where relationships between the four variables was identified directly from the data. Due to the irregularities in the data, the speaker was interested in modeling the general trend of the data and not the daily fluctuations and data averaged over 7 days. The revised model provided good fits to the average data and has suggested improvements to how the data collected for future model iterations.

Static and dynamic phenotypes in sepsis

Gilles Clermont (University of Pittsburgh)

Dr. Clermont discussed sepsis, a highly morbid and mortal syndrome accompanying severe infections often requiring intensive care. Since sepsis presents itself in a number of different ways, it is a preferred target for personalized medicine, as different phenotypes might require entirely different interventions. Dr. Clermont first discussed ways to understand static data from a recent large randomized sepsis trial, where they used a hierarchical clustering method to separate patients into distinct phenotypes using observables such as cytokines, vital signs, and cell counts. The heat maps obtained using appropriate cluster aggregation revealed distinct populations within septic populations and suggested that people with high cytokinemia were at higher risk. He then discussed the idea that different dynamic septic phenotypes may translate into different cytokine trajectories. Using these trajectories, they concluded that clinical differences can appear within six hours of sepsis. Finally, they developed an endotype prediction algorithm using random forests and plan to improve the clinical relevance of this model.

Quantitative systems pharmacology modeling enables personalized anemia treatment

Bernhard Steiert (Albert-Ludwigs-Universit at Freiburg)

Dr. Steiert began his talk with schematics to motivate how cells act as an information processing system, where the intracellular signals lead to cell phenotypes. This talk was particularly concerned with how biochemical reaction dynamics that occur about cell receptors are bound by ligands like drugs. The key application here was anemia treatment Erythropoietin (EPO) and Erythropoietin stimulating agents (ESAs) entering the blood stream and how they bind to red blood cell receptors. The speaker introduced a mechanistic cell-scale model of erythropoiesis (red blood cell development) to investigate how receptors are responsive over a wide range of ligand and then presented four possible mechanisms for this robustness. To parameterize the model, maximum likelihood estimates were used initially and a profile likelihood improved estimates of the parameters one-at-a-time. Dr. Steiert showed plots of the concentrations of EPO receptors over time to investigate which model mechanisms were plausible. The analysis found that receptor turnover was the key mechanism that drove the observed linearity between the EPO concentration and the EPO receptor activation. Next the speaker sought to connect modeling at the molecular scale with pharmacokinetic-pharmacodynamic data from different patients. Considering multiple patients required mixed-effects modeling and found that the number of ESA binding sites and hemoglobin degradation rate needed to be patient-specific parameters and were fit with patient datasets. Finally, the speaker discussed next steps needed to develop an online personalized anemia management platform that physicians can use.

Engineering Glucose Control Solutions for Intensive Care Patients
Robert Parker (University of Pittsburgh)
Dr. Parker talked about a condition known as "stress hyperglycemia" in ICU patients, which has been tied to increased clinical mortality and morbidity, as well as longer ICU stays. He mentioned that controlling glucose to the normoglycemic range comes at a price, since there is an increased probability of hypoglycemia, where a single event is an independent driver of morbidity in critical care patients. He discussed the issues and challenges in synthesizing a glucose control decision-support system for use in the critical care setting. They used nonlinear dynamic mathematical models such as the intensive control insulin nutrition glucose model and created virtual patients based on critical care data. They then designed a dual-input model predictive control scheme that uses insulin to control glucose, and glucose infusion to mitigate hypoglycemia. He also discussed issues with the quality of glucose sensing in continuous glucose monitoring (CGM). Using a sensor fusion algorithm, they characterized the errors in these CGM measurements in the ICU setting. Dr. Parker showed the effectiveness of the control system on "virtual patients", based on a parameter set derived from clinical ICU data from patients at University of Pittsburgh Medical Center.

An Optimal Control Approach to Structured Treatment Interruptions for HIV Patients: A Personalized Medicine Perspective
Hien Tran (North Carolina State University)
Dr. Hart discussed how for many patients, long term continuous HAART (Highly Active Antiretroviral Therapy) is expensive and can lead to drug toxicity and side effects, as well as increased drug resistance. Some HIV infected patients voluntarily terminate HAART or interrupt the continuous prescribed therapies for short or long periods. After discontinuing HAART, patients will usually experience a rapid increase in viral load coupled with a immediate decline in CD4+ counts. He mentioned the canonical example of a patient undergoing unsupervised breaks in HAART: the Berlin patient. In this case, the patient controlled viral load in the absence of treatment by cycling HAART on and off due to non-related infections. Dr. Tran was therefore

interested in using HIV models and an optimal control approach to determine structured treatment interruptions (STI) regimens as a mechanism to regulate an HIV infection. He used a nonlinear differential equations model for the in-vivo dynamics of an HIV type 1 infection. For the available clinical data, he used expectation minimization to predict missing data from sensor observations. They then calibrated the model by estimating on a patient specific basis a subset of parameters using sensitivity analysis and subset selection. The optimal STI was implemented in the context of the receding horizon control (RHC), and they found that frequent cycles of treatment interruption lower the viral load considerably. They concluded that customized STI protocols can be designed through the variation of control parameters on a patient specific basis.

Modeling the Coupled Leukemic-Inflammatory Responses with application to treatment planning

Johnny Ottesen (Roskilde University)

Dr. Ottesen began with an overview of stem cell proliferation to motivate how malignant stem cells divide in a more uninhibited manner than normal hematopoietic stem cells. In addition, he discussed results from the literature that both proposed inflammation to be a cause and effect of cancer. The speakers group south to explain the inflammatory component of cancer and built on an established model of hematopoiesis by adding in pro- and anti-inflammatory dynamics. The established model was compartmental with four states: normal or tumor cell and either differentiated or stem cell. Mutation from either normal stem or normal differentiated cells was modeled by a poison process. The addition of pro- and anti-inflammatory effects, representing cytokines released during an innate immune response, were coupled to the compartmental model bringing the final model up to six dimensions. Dr. Ottesen considered stability analysis and found five steady states; the analytic expressions for the steady states and their stability suggest application of control theory could help steer towards the most desirable state. The introduction of immune responses led to time scale parameters, that the speaker exploited these time scales to reduce the model to two dimensions via geometric singular perturbation theory. The validated reduced model will be more suitable for optimal control purposes since dynamics can be studied in the plane.

WEDNESDAY, NOVEMBER 1, 2017

Safety by design: what can we do to make automated drug delivery in anesthesia safe?

Guy A. Dumout (The University of British Columbia)

Improving patient safety is always a key focus in the hospital setting. In anesthesia, automated feedback control holds the promise of limiting the effects on performance of the individual patient variability, optimizing the workload of the anesthesiologist, increasing the time spent in a more desirable clinical state, and ultimately improving the safety and quality of anesthesia care. With feedback, one can build high-performance systems from imperfect, imprecise components and even imperfect models. The goal is to control the entire closed loop process and create a new devise without delays. For clinical adoption to take place, benefits to the patient have to be demonstration while patient safety is guaranteed. This presentation describes the engineering design theory of robust control and demonstrates its use for closed-loop anesthesia in order to guarantees stability and a minimum level of performance acceptable to the clinician.

Augmented clinical decisions

Mark Ansermino (The University of British Columbia)

Effective use of the information produced by current and future physiological sensors can be used to improve monitoring, diagnosis, and treatment of patients. The successful introduction of intelligent monitoring and automated control promises to harness this information can enhance patient safety. Though intelligent data analysis requires a multifaceted approach, supported by powerful data driven by prediction models. A range of techniques are used, including statistical characterization, modeling, feature extraction, and prediction. Most importantly, early identification of the patient at risk can change healthcare behavior and allow for early referral when a higher level of care is required. This talk presents an effort to embrace intelligent monitoring and automated control, with the goal to significantly change the trajectory of the typical disease process.

Multivariable modeling and control approaches for anesthetic pharmacodynamics
Carolyn Beck (University of Illinois at Urbana-Champaign)
Engineering and control technology have played a major role in medicine over the past half-century and continue to play a major role. Modeling and control of drug dosing in clinical pharmacology is one area of medicine in which mathematical modeling is used extensively, and hence is well-suited for applications of control design and analysis techniques. This presentation provides an overview of some robust and adapt approaches to the problem of controlling patient response to relative anesthetic agents in clinical settings. In current practice, anesthesiologists perform the role of a multivariable feedback controller for a highly complex process. The goal is the incorporate partially automated anesthesia delivers into the process, allowing the anesthesiologist to concentrate on urgent safety-critical events that arise during surgery. The construction of a multivariable patient model is discussed as well as the application of advanced control methods.

Modeling the control of cardiovascular dynamics during orthostatic stress
Nakeya Williams (United States Military Academy)
Orthostatic intolerance (OI) is an inadequate balance of blood pressure (BP), blood flow (F), and heart rate (HR) level upon standing with alleviation of symptoms upon recumbency. It is poorly understood and hard to diagnose and treat. The goal of this work is to develop simple patient models that accurately depict the beat-to-beat dynamics that clinicians can use to efficiently assess individual patients and predict changes in arterial blood pressure. The purpose is to reproduce the patient's problem in a controlled laboratory setting to gain knowledge on what cardiovascular mechanisms are affected and what treatment options are best for the specific patient.

Controls of a cardiovascular-respiratory systems under ergonometric workload
Aurelio de los Reyes V (University of Philippines)
The human cardiovascular system (CVS) and respiratory system (RS) work together in order to supply oxygen and other substrates needed for metabolism and to remove carbon dioxide. Global and local control mechanisms act on the CVS in order to adjust blood flow to the different parts of the body. This, in turn, affects the RS. A model of the human cardiovascular-respiratory system (CVRS) is developed to describe its response to various ergonometric workloads. An optimal control for time-varying workloads is obtained by using the Euler-Lagrange formulation of the optimal control problem. The essential controls in the CVRS model are variations in the heart rate and alveolar ventilation through which the central nervous system restricts the arterial partial press of carbon dioxide. Further, penalization terms in the cost functional are included to match the metabolic need of oxygen and the metabolic production of carbon dioxide, including transport by

blood. Lastly, a sensitivity analysis is performed and parameters are estimated indicating good fitting results.

THURSDAY, NOVEMBER 2, 2017

Hybrid multi-scale models explain emergent dynamics in heterogeneous cell populations
Neda Bagheri (Northwestern University)
Dr. Bagheri talked about her lab's use of computational modeling for integrating and understanding complex biological systems. In particular, they are interested in using the increasingly high-resolution, high-throughput, and dynamic experimental data to develop better informed models to interrogate the complex, heterogeneous, and multiscale nature of cellular microenvironments. She focused on using a dynamical systems and agent-based model to study emergence in a cancer, where many heterogeneous cell populations are involved. She discussed an agent-based model through which they investigate the impact of intracellular network dynamics on intercellular signaling in the context of cancer, with future applications to personalized medicine. This multiscale model accounted for network dynamics (nonlinear ODEs), cell agents (rule-based), diffusion and vasculature (flow equations). They checked the model against certain measures such as circularity as well as the maintenance of a proliferative rim of cancer cells. They also noticed that coupled vascular dynamics were critical to recovering the necrotic rim. Dr. Nagheri concluded that agent-based models may be computationally expensive for control, and that an appropriate cost function must be developed.

Controlling acute inflammation: a summary of strategies
Judy Day (University of Tennessee)
Dr. Day discussed talked about dysregulation of the natural processes that govern the inflammatory response to severe infection or traumatic insult (acute inflammation). She mentioned that intervention is necessary to restore homeostasis to the host, but that knowing how to intervene in order to help guide desirable outcomes is a difficult endeavor due to the complexity of the immune response. She used a canonical and highly nonlinear mathematical model of the systemic acute inflammatory response that accounts for positive and negative feedback loops of inflammatory responses. This model exhibits three clinically relevant stable states. Using this model, they investigated and compared different control strategies to determine therapeutic intervention protocols to control acute inflammation to a desired state.

She also focused on results of several methods applied in a diverse virtual patient population with limited measurement feedback. These methods use nonlinear model predictive control combined with state estimation, optimal control, and a newer method called model free control, and the determined control therapy was shown to increase percentage of predicted healthy populations.

Cardiovascular control in patients with orthostatic intolerance
Mette Olufsen (North Carolina State University)
Dr. Olufsen introduced data such as time-series signals including heart rate and blood pressure that can help determine the state of the cardiovascular system, as well pathophysiology. She proposed that analysis of this data with computational models can uncover the underlying mechanisms driving these dynamics. She focused on the application to dynamics observed in patients diagnosed with postural orthostatic tachycardia (increased heart rate brought on by change in posture, e.g. sit to stand), observed in some girls after vaccination against the human papilloma virus (HPV). In

several studies, girls exhibiting side-effects to this vaccine often feel dizzy, light-headed, and tired. To understand how these symptoms are related to pathophysiology within the cardiovascular control system, Dr. Olufsen used models to analyze patient specific changes observed during head-up tilt, Valsalva (breath holding), and deep breathing. In head-up tilt, they could reproduce syncope (fainting) by introducing several control components. In Valsalva, their detailed cardiovascular mathematical model could characterize the responses by distinguishing between different baroreceptors. In addition, these models can predict the emergence of oscillations in girls with postural orthostatic tachycardia. She also discussed how mathematical modeling can be adapted to match patient specific behavior and how the optimized system equations can be used to predict emergent behavior. She described tools such as sensitivity analysis, parameter estimation, and uncertainty quantification used to analyze models for individual patients.

Novel intoxication treatment: an application of mathematical model and multi-objective optimization
Vaibhav Maheshwari (Renal Research Institute)
Drug intoxication is a huge problem as the 8th leading cause of death in the United States. The best treatment option of intoxication is hemodialysis (HD), but HD has a strong protein-binding and thus not so efficient in removing protein-bound drugs. A recent novel concept is presented, using a displacer infusion which competes with protein-binding so that the toxin will be free to remove. This talk presents a partial differential equation model for HD and displacer infusion, treated as a multi-objective optimization. A model patient of intoxication is treated, showing that the displacer augmented HD allows use of HD, even when it is usually neglected due to strong protein-binding of the drug. Also it is shown that the displacer reduced the HD time and thus side-effects of the intoxication drug.

Control of anemia in hemodialysis patients: an MPC approach for optimal EPO dosing
Sabrina Rogg (Fresenius Medical Care Deutschland GmbH)
Hormone EPO (erythropotetin) is produced in the kidneys and drives production of new red blood cells. Chronic kidney disease occurs due to an insufficient release of EPO resulting in chronic anemia. Anemia management with EPO is a challenge in hemodialysis (HD) patients since their response to treatment varies greatly. This talk describes a model for a predictive control algorithm for the individualized dose optimization. Computer simulations are conducted to test this method against the standard dosing protocol for a cohort of 60 HD patients. Looking at this method model based, it works better than the standard protocol even in simulations with missed treatments and bleedings.

Open versus closed loop control in a respiratory model
Peter Thomas (Case Western Reserve University)
The general framework of biological rhythmic control problem deals with breathing, walking, swimming, flying, as well as chewing and swallowing. A closed-loop respiratory control system is created incorporating a central pattern generator (CPG), the Butera-Rinzel-Smith model, together with lung mechanics, oxygen handling, and chemosensory components, to compare with an open-loop (isolated) model. Neuronal activity is described by an autonomous central pattern generator and motor system variables are driven by neuro/biomechanics and external loads. Sensory feedbacks are also incorporated to regulate central pattern generators. Although both closed-loop and open-loop CPG systems support eupnea-like (normal breathing) activity, they do so via distinct mechanisms. Closed-loop respiratory control gives greater robustness, but also leads to

instability. In addition they show that the classical central pattern generator model also has the capacity to support auto-resuscitation.

FRIDAY, NOVEMEMBER 3, 2017

Limited Epitopes and Age-specificity: Heterogeneity in immunity shapes strain-structured influenza epidemics and the impact of vaccination
Alhaji Cherif (Renal Research Institute)
Dr. Cherif talked about how controlling infectious disease of antigenically variable pathogens faces significant challenges in overcoming persistence, emergence and re-emergence mechanisms, circumventing behavioral and transmission bottlenecks, and targeting high-risk core groups for prophylactic strategies and therapeutic interventions. In his talk, he discussed the new hypothesis of limited epitopes or antigenic drift. The modeling framework proposed includes age-structured multiple strains of disease (network of populations), with contact rates between age groups and an SIR modeling approach. He discussed tools for model analysis stemming from graph theory as well as dynamical systems (stability of equilibria, bifurcation analysis of the reproductive number R0). He then showed the good agreement of this model when applied to influenza data, and discussed public health implications such as vaccination of different strains. Based on this modeling effort, he suggested the use of robust differential/dynamic intervention strategies depending on age-specific and antigenic cluster-specific immunological profile of the population.

Patient Specific Cardiovascular Systems Modeling: Deep Phenotyping using Deidentified Clinical Data
Brian Carlson (University of Michigan)
Dr. Carlson described how clinicians evaluate cardiovascular function in patients with a variety of clinical measures including right heart catheterization (RHC) and echocardiography measures of cardiac pressures and chamber volumes. These measurements inform clinician decisions concerning cardiovascular diseases such as pulmonary hypertension and heart failure with preserved ejection fraction. He proposed using a retrospective approach where clinical data and computational models may allow to make patient-specific decisions. In his talk, he focused on using a cardiovascular system model with ventricular-ventricular interaction and RHC measures from heart transplant patients to capture cardiovascular system function and track it over the recovery from heart transplantation. The clinical data used in his work came from a deidentified clinical data repository at the University of Washington and contained only minimum and maximum pressure at several locations in and around the heart along with cardiac output. Despite having a differential-algebraic system of equations with many parameters, Dr. Carlson described the choice of a subset of parameters to optimize to the data using methodology such as the DRAM sampling method and subset selection. He showed examples where they have identified the model for 10 patients and have begun identifying the models to data from follow up visits for each of these patients. He illustrated parameterizations of several sets of patient data, which exhibited a breadth of behaviors. Finally, he explained how the predicted function could be used by cardiologists as an additional guide for heart transplant evaluation and follow up treatment.

An assessment of model-based in silico clinical trials
Doris Fuertinger (Fresenius Medical Care)
Dr. Fuertinger described in silico clinical trials, which are realistic computer simulations of clinical trials that can be used to provide valuable information regarding safety and limitations of treatment

protocols and have been shown to be vital for the cost-effective planning of clinical studies. She explained that Monte Carlo sampling and re-sampling techniques are frequently used to create virtual populations for this purpose, but that these simulations may not represent the (patho)physiology of an actual individual subject, because, only population-wide characteristics are represented. Thus, randomized controlled trials have to generally pass internal, external and ecological validity tests. She then showed how patient-level data can be used to create large cohorts of individual virtual representations of patients ("Avatars") aimed at anemia dosing and administration strategies in hemodialysis patients (The Virtual Anemia Trial). The model used for these in silico trials used equations for age-structured cell populations and was validated using different data. To create the "avatars", they used parameter vectors from a priori known parameter distributions, and made sure that population characteristics such as hemoglobin levels and frequency of dose administration agree. Their simulations at the patient level are compared to empirical data of 79,426 HD patients. In addition, she touched on the topic of ecological validity of Virtual Clinical Trials (VCT), for which they integrated clinical modules in the trial simulations (accounting for hospitalization, dialysis facilities, etc. in a stochastic manner). She concluded that the strategies proposed, aimed to improve external and ecological validity of the VCT, can significantly increase the predictive power of the discussed in silico trial.

Autumn Workshop 4: Sensori-motor Control of Animals and Robots (November 13-17, 2017)

Organizers: Manoj Srinivasan (The Ohio State University), William Warren (Brown University)

Report by: Punit Gandhi, Colby Long, Alexandria Volkening

MONDAY, NOVEMBER 13, 2017

Learning to Walk: Babies and Bots
Karen Adolph (New York University)
Studying how infants walk can inform bot research by helping experimentalists identify the problems new walkers naturally encounter; moreover, the way babies solve these problems can offer additional insight into designing systems that can learn to walk. With this as motivation, Dr. Adolph observes how infants walk in test rooms in her experimental studies. While the traditional approach in her field is to track infants stepping on treadmills or walking continuously along straight, forward paths over uniform ground, she recognized that infants do not display such standardized gaits in the real world. Instead, her observations of infants walking in her test room show that their movement is punctuated with frequent starts and stops. Additionally, her videos of young walkers show infants choosing variable, curving, twisty paths that include steps in all directions, not just forward.

Dr. Adolph found that the variability she observed in natural walking patterns did not change over development, and she noted that it was similar to optimal foraging in animals (which can be described by Levy walks). She argued that this variability is crucial: in particular, varied experience may promote behavioral flexibility. In fact, soccer-playing robots trained on similar kinds of varied walking styles won the Robo Cup, further suggesting that varied experience leads to higher functional consequences. Thus, in response to the question *how do we design a system to learn to walk?*, Dr. Adolph suggested we study infants learning to walk: their functional, adaptive

locomotion requires large amounts of varied experiences as they adapt to their changing bodies in their changing environments.

Learning to walk economically
Max Donelan (Simon Fraser University)
People prefer to exhibit gaits that minimize their energetic cost, with low and high step frequencies more costly than middle-ground behavior. In the beginning of his talk, Dr. Donelan asked over what time scale humans prefer to adapt their gaits to minimize energy expense: does this adaption occur over evolutionary or developmental time-scales, or in real time, with walkers continuously optimizing their energetic cost? To answer these questions, Dr. Donelan and his colleagues fit people with an exoskeleton that reshapes their energy landscape by resisting knee motion, mechanically adding a penalty either to lower or higher step frequencies.

Observing people walking on treadmills while wearing these exoskeletons, Dr. Donelan's lab found that people can rapidly converge upon energetically optimal gaits when exposed to new energetic landscapes. This convergence could conceivably occur by various mechanisms: it could be spontaneous, for example, or be through broad explorations of the energy landscape. His experiments show that humans exhibit a gradual local search to find new energetic optima. However, he also studied the effect of applying horizontal (pulling or pushing) forces on walkers, and he found that people do not optimize energy in this setting. This suggests a venue for future study, as there may be more to learn about energy optimization by understanding the settings in which humans do not adjust their gaits in response to new energy landscapes.

Feedback and feedforward learning in sensorimotor control
David Franklin (Technical University of Munich)
In his talk, Dr. Franklin discussed the results of several recent experiments on the formation and recall of motor memories. In each of the experiments, subjects made movements in a velocity-dependent curl field under a variety of conditions. The subjects were tasked with reaching in a particular direction and learning was measured by their ability to compensate for the applied forces. When the subjects were provided with visual feedback and the field was always applied in a consistent direction, then they quickly learned the field. However, if the direction of the field was randomly varied, then subjects were completely unable to learn. Interestingly though, if the subjects were asked to perform a motion prior to entering the force field that corresponded to the particular direction of the field, then they learned to navigate both fields quickly. These results suggest that prior motion causes the formation of two different active motor memories.

Dr. Franklin also discussed several other modifications to the above experiment designed to give insight into how motor memories are formed in the presence of sensory feedback. For example, in visually guided reaching exercises, the researchers perturbed both the location of the target and the visual feedback that subjects received. The measured rate of learning under these conditions can be tested against various models of how sensorimotor memories form to challenge or validate the existing models.

Running in style, staying balanced, and getting a grip in simulated control
Paul Kry (McGill University)
Equipping simulated humans and animals with the ability to locomote and interact within physics-based simulations presents a number of interesting challenges. While there are obvious immediate

applications of such work to computer imaging and graphics, understanding these problems will likely also help with the development of prostheses capable of natural motion. In his talk, Dr. Kry described work on three specific challenges: controlling style in locomotion, anticipation during balancing, and control for in-hand manipulation.

The project he described in most detail involved controlling the style of locomotion for animals in simulations. Typically, one might consider manually designing the control system, finding an optimal control system through optimization, or discovering an optimal control system through a data driven approach. Of course, if data for the animal is completely unavailable (such as for extinct species), the last approach is impossible. Instead, Dr. Kry described how he and his collaborators they modal analysis by treating the animal as a physical system. First, they imbued the joints of the animals with parameters for stiffness, flexibility, and range of motion. They then combined simple modes with heuristics to produce kinematic locomotion. After briefly describing the other two projects, he also discussed some ongoing efforts to learn control strategies from captured motion.

Experiential approaches to artificial haptic perception and decision-making for grasp and manipulation

Veronica Santos (University of California, Los Angeles)

There are many situations where tactile sensing provides the primary or even sole source of information during grasp and manipulation tasks. Dr. Santos described her group's efforts to automate certain aspects of such tasks using hand-like robots equipped with tactile sensors. In this way, the robot can take complete tasks suited to self-automation and report to the human controller for further instructions on how to proceed when input is needed. She discussed studies to achieve goals like closing a ziplock bag or searching for buried or submerged explosive devices. The real-time decision-making algorithm is based on a resource-conscious, "multi-armed bandit" approach that first explores the potential state space to see how actions are rewarded and then selects actions that exploit the learned reward policies to maximize gains.

Haptic communication between humans and with robots

Etienne Burdet (Imperial College)

Dr. Burdet reports on an experiment that uses a dual robotic interface to investigate how humans perform on collaborative motor tasks. The goal of the two subjects in the experiment was to track a target on a screen with a joystick-controlled cursor and each subject could only see their cursor and the target. A computer controlled force could be applied to the joysticks that simulated a Hookian spring force between the cursors of the two subjects. The result of the experiment was that connecting a subject's cursor to a partner with a spring force resulted in improved performance regardless of whether the partner performed better or worse than the subject when not connected. Dr. Burdet noted that even if the partner is worse than you at tracking the target, you are still gaining information from the interaction force. He also contrasted this kind of haptic communication where each subject feels the forces directly to verbal communication where the subjects can lie and trust becomes an issue. He pointed out that children often play games that rely on haptic communication through touch, speculating that the results of these experiments may be relevant. Finally, he suggested a potential application to physical therapy where the therapist and patient or even two patients collaboratively work on a motor task together.

TUESDAY, NOVEMBER 14, 2017

Legged locomotion: what's vision got to do with it?
William Warren (Brown University)
Biology exploits both physics and information (e.g. acoustic and optic signals). As Dr. Warren noted, agent behavior is not simply prescribed entirely by a controller but emerges from the dynamics of the agent-environment system: in particular, the environment acts on the agent by providing information through the laws of control, and the agent responds with an action through the laws of physics. He claimed that information modulates agent dynamics to yield behavior that is both stable and adaptive to a complex, changing environment. While proprioception provides short-range reactive control, vision enables longer-range prospective control and reduces the impact of local perturbations. Dr. Warren went on to review experimental evidence showing that human movement is controlled by visual information at every level of the hierarchy. Notably, people need to see 1.5 steps ahead in order to successfully land their feet on targets. Similarly, when walking slalom, people steer 1.5 targets ahead in simulations. Interactions with other individuals are also modulated to generate collective motion in bird flocks and human crowds.

Active and passive control of bipedal walking over complex terrain
Brett Fajen (Rensselaer Polytechnic Institute)
Real world terrain poses many potential challenges for systems, both animals and robots, that move about by means of bipedal locomotion. Nevertheless, humans and other bipeds are quite capable of negotiating irregular terrain without risk of injury and without giving up on the strategies that make them stable and efficient walkers on flat, uniform surfaces. In his talk, Dr. Fajen explored how humans blend active and passive modes of control as they adapt gait to the layout of the upcoming terrain, cross obstacles, and land on safe footholds.

He described what he termed the "the perception-action coupling account" which holds that people walk by receiving information and applying some control law to determine what action to take. However, as he explained, this model is agnostic as to whether the information is received intermittently or continuously. He then presented results from some of his lab experiments which he argued demonstrate unequivocally that humans use intermittent visual gait regulation as opposed to continuous. He concluded by discussing future challenges, such as determining why visual gait regulation should be intermittent. He also mentioned some of the important take-aways from this research for attempts to close the gap between humans and bipedal robots.

Multisensory integration for fly flight
Jessica Fox (Case Western Reserve University)
Animal behavior frequently requires the integration of information from multiple sensory modalities. In many moving animals, vision is a dominant modality, but visual information is only useful for movement in the context of the body's own position and motion. How do animals integrate visual motion with proprioception and mechanoreception to coordinate their movement? In flies (Diptera), specialized hindwings known as halteres detect body rotations and guide wing steering and head movements.

In her talk, Dr. Fox presented some of her research using quantitative behavioral analysis and electrophysiological recordings to examine how the fly nervous system uses visual and mechanical information to coordinate specific behaviors. In most of the experiments, the responses of flies exposed to various stimuli were measured and compared against those of a group of flies with their

halteres removed. She showed that the influence of halteres on both wing steering and head movement behavior is dependent on behavioral and visual context. Her results suggest a cross-modal role of haltere input on visually guided behaviors.

Training underwater sensory arrays using neural networks
Eva Kanso (University of Southern California)
Unsteady flows contain information about the objects creating them. Detection of these hydrodynamic cues is relevant to many biological and engineering applications including underwater navigation. Aquatic animals offer intriguing paradigms for extracting flow information from local sensory measurements. In contrast, classical methods for flow analysis and classification require global knowledge of the flow field. In her talk, Dr. Kanso described her work leveraging techniques from artificial neural networks to develop a data-driven approach for flow classification based on local flow measurements and applying it to vortex wakes behind an oscillating airfoil. She then compared this approach to physics-based models for decoding sensory information and commented on the pros and cons of both models.

From Simple movements to complex skills: a task-dynamic approach to motor control
Dagmar Sternad (Northeastern University)
Much of traditional and current research on motor control and neuroscience has analyzed highly simplified movements in tightly controlled experimental paradigms to permit rigorous analysis. In contrast, movement and sport science have emphasized complex actions in highly skilled performers. Dr. Dagmar presented a task-dynamic approach that starts with analysis of how the task constrains and enables actions and their improvement with practice, in order to facilitate insights into complex actions. She discussed three exemplary tasks of throwing a ball, rhythmic bouncing of a ball, and transporting a "cup of coffee" in order to illustrate the approach. In each case she presents a simple mathematical model of the task and then argued that humans develop skills to meet the complex demands of the task by: 1) finding error-tolerant strategies and channeling noise into task-irrelevant dimensions, 2) exploiting solutions with dynamic stability, 3) optimizing predictability of object dynamics.

Dynamic primitives for movement control
Neville Hogan (Massachusetts Institute of Technology)
Despite vastly slower "hardware" (e.g. muscles) and "wetware" (e.g. neurons), human dexterity and agility significantly out-performs contemporary robots. Dr. Hogan tried to address the question of how this is possible in this presentation. He argued that such success in the face of slow actuators and long communcation delays require predictive control based on some form of internal model, and one possiblity is a model based on dynamic primitives (attractors). The advantage of such a model is that dynamic primitives enable highly dynamic behavior with minimal high-level supervision and intervention. Dr. Hogan proposed three primitives as a foundation for a comprehensive theoretical framework that can embrace a wide range of upper- and lower-limb behaviors: submovements, oscillations and mechanical impedences. Submovements and oscillations are motion primitives while impedenances are required for controlling interaction with the physical environment. These primitives may be combined by a nonlinear generalization of the classical equivalent electrical circuit.

Symmetries of Solutions; Symmetries of Models
Marty Golubitsky (The Ohio State University)

The walking patterns of 4-legged animals come in different forms, including trotting, pronking, walking, pacing, and bounding. These quadrupedal gaits can be defined by their spatio-temporal symmetries. For example, in a trotting gait, the front left and right hind legs move synchronously, the front right and the left hind legs move at the same time, and there is a half-period phase-shift between these two sets of legs. Noting that a network of neurons (the central pattern generator) produces gait rhythms, Dr. Golubitsky asked if you can design a simple 4-node network of differential equations that can produces walk, trot, and pace gait patterns with the appropriate symmetries. He found that you need 8 nodes to do so: prescribing two controllers per leg (corresponding to the two muscle groups of each joint) was able to produce solutions with correct symmetries. In a different applied direction with a similar mathematical framework, Dr. Golubitsky also discussed homeostasis; this is the phenomenon where you can vary an input parameter over a fairly large range (e.g. external temperature) and the system (e.g. internal temperature of an organism) remains pretty constant. The bifurcation diagrams for systems in homeostasis look chair-like, with a large horizontal area flanked by two regions of escape from homeostasis. Dr. Golubitsky noted that homeostasis is not something that can be attributed to a large class of differential equations; instead, it is an emergent property of biochemical networks.

WEDNESDAY, NOVEMBER 15, 2017

Energetic basis of human locomotion and behavior
Arthur Kuo (University of Calgary)
One way to understand sensorimotor control in living organisms is to view motion as the solution to an optimization problem. In fact, this is the approach that many researchers take when studying motion and it has useful applications. For example, it can be shown that humans adjust their step length and step frequency in order to minimize the energy costs incurred in covering a certain distance. However, in his talk, Dr. Kuo discussed some of the difficulties that are inherent in adopting an optimization perspective. He also reinterpreted some of the experiments that are traditionally seen to validate the optimization perspective and questioned some of the underlying assumptions.

To define motion as the solution to an optimization problem, we must define both an objective that we wish to achieve and a cost function associated with achieving the objective. Dr. Kuo argued that any reasonable cost function must account for the cost of control, otherwise, it can be shown that that the optimal motion is always to move as quickly as possible. But, there are also many other costs that are typically not taken into account when studying motion. For example, there are psychological costs, as people are inclined to try to interpret the desires of the experimenters in lab settings. There are also reward costs, as the objective at the end of the task may motivate people to move at different speeds. Thus, a purely physical model that only considers physiological energy expenditures is unlike to accurately predict the ways in which people move.

The search for a simple balance control that is both robust and energy-stingy
Andy Ruina (Cornell University)
In his talk, Dr. Ruina first summarized the primay goal of the field of sensorimotor control. That goal he broadly defined as trying to make or understand a controller or control system of either a robot or animal that does not fail (i.e., fall) and that does not use too much energy. He then discussed his specific goal, which is to make a bipedal robot capable of realistically mimicking human walking. His team has built a robot, which they have dubbed Tik-Tok, using powerful,

light, and energy efficient motor controls. These motors allow the robot to achieve very rapid step times which Dr. Ruina believes is one of the key features that contribute to robustness. Similarly, his team has designed Tik-Tok with extremely low friction bearings and energy efficient transmission to achieve a cost of transport that is lower than that of any other bipedal robot and that is on par with that of actual human beings.

He then discussed the means of controls used to stabilize Tik-Tok and prevent the robot from falling down. The particular approach his team uses is a form of dimension reduction to reduce the size of the control problem involved in stabilization. They represent the current state of the robot using only a small number of variables and optimize to determine the necessary actions to achieve balance and control. He concluded his talk by comparing and contrasting the means of control used in robots to those used in biological systems.

Towards a unifying framework for decision making and movement control
Alaa Ahmed (University of Colorado Boulder)
Decisions depend on the reward at stake and the effort required. However, these same variables influence the vigor of the ensuing movement, suggesting that factors that affect evaluation of action also influence performance of the selected action. To illustrate this point in her talk, Dr. Ahmed used the example of a person deciding whether to reach for an apple of for a cookie. We might expect that the reward at stake is greater when the person is reaching for a cookie. Consequently, we might expect that the ensuing movement towards the cookie will be more vigorous than for the apple.

Dr. Ahmed went on to describe a mathematical framework that links decision-making with motor control. Each action has a utility that combines the reward at stake with its effort requirements, both discounted as a function of time. The critical idea behind this model is to represent effort via the metabolic energy expended to produce movement. She showed that a single mathematical formulation of action predicts both the decisions that animals make as well as the vigor of the movements that follow. This framework accounts for choices that birds make in walking vs. flying, choices that people make in reaching and force production, and the curious fact that pedestrians walk faster in certain cities. Her work suggests that decision-making and movement control share a common utility in which the expected rewards and the energetic costs are discounted as a function of time.

Progress in Human-in-the-loop Optimization of Exoskeleton Assistance
Steve Collins (Stanford University)
Exoskeletons and active prostheses promise to enhance human mobility, but few have succeeded. Optimizing device characteristics on the basis of measured human performance could lead to improved designs. In his talk, Dr. Steve Collins presented a method his lab has developed for identifying the exoskeleton assistance that minimizes human energy cost during walking. Optimized torque patterns from an exoskeleton worn on one ankle reduced metabolic energy consumption by 24.2-27.4% compared to no torque. The approach was effective with exoskeletons worn on one or both ankles, during a variety of walking conditions, during running, and when optimizing muscle activity. Finding a good generic assistance pattern, customizing it to individual needs, and helping users learn to take advantage of the device all contributed to improved economy. Dr. Collins concluded his talk by describing some ongoing follow-up work and discussing opportunities for further improving the design of exoskeletons and prosthetic limbs.

Life in rough terrain: Integration of mechanics and sensorimotor control for agile and robustly stable bipedal locomotion

Monica Daley (Royal Veterinary College)

Animals must precisely control limb-substrate interactions to move effectively over varied and uncertain terrain while avoiding injury. Dr. Daley discussed experiments in which ostriches are presented with unexpected perturbations to terrain. The ground birds were able to recover from a camouflaged step down and step up in height within about two steps. The tradeoff in navigating the unexpected change between ensuring contact between the foot and ground to avoid falling and stepping to reduce the load on the leg and avoid injury. The experiments indicate that the swing leg control priority of the ostrich is to maintain a consistent peak force on the leg. Dr. Daley also discussed a second experiment to track a flock of ostriches in the field. Her team was able to measure walking/running gate, velocity and step size in addition to spatial location. The ostriches were found to have a very tight preferred walking speed which is close to optimal based on an inverted pendulum model. This is in contrast to people who tend to walk faster than optimal.

Flight control with hairy, skin-ny wings: gust perturbation recovery and landing dynamics in bats

Sharon Swartz (Brown University)

Dr. Swartz talked about a study of flight control in bats. The critical non-equilibrium flight performance tasks of interest were: 1) coping with transient but large magnitude variations in ambient airflows, and 2) landing, a task that is particularly challenging for bats, who when landing on ceilings must simultaneously ascend, decrease in speed, and reorient the body from head-forward to "head-under-heels". She showed that following substantial gust perturbations of up to 2.5X body weight to one wing, bats undergo significant body roll and employ left-right asymmetrical wing kinematics, then recover body orientation, stable trajectory, and symmetrical wing motion, typically within a single wingbeat cycle. Dr. Swartz suggested that bats have unique arrays of hair sensors and actively modulated, variable wing membrane skin stiffness that contribute their ability to handle these tasks in a robust way. She also argued that passive mechanical and inertial characteristics of the bat's wing structure may be critical as well. Finally, she discussed a survey of landing dynamics in diverse bat species that suggests transitions from less- to more finely-controlled landing dynamics (lower impact forces, higher rotational complexity) have occurred multiple times during bat evolution.

Optimization of Bipedal Walking in an Uncertain World

Katie Byl (University of California, Santa Barbara)

Much work has been done in optimizing nominal limit cycle walking trajectories for minimal energetic cost. Dr. Byl discussed the complementary (and mathematically messier) goals of improving robustness through optimization both of passive mechanical impedance properties and of parameterized feedback control policies in order to cope with unexpected perturbations, terrain variability and/or noisy sensing of absolute orientation within a world frame.

The main hypothesis of the talk was that one needs to optimize a combination of energy cost, robustness, and agility, speed or other relevant factors for bipedal walkers on uncertain terrain. Dr. Byl defined agility as the ability to reach a large portion of the state space from the current agile state. In contrast, she defined robustness as the ability to get to a target robust target state from a large region of the state space. A trade-off between robustness and agility must be considered

when maximizing a system with passive control versus active control. She gave the example of a glider and airplane: The glider's state should be robust because it should remain in flight despite perturbations from the environment. The airplane on the other hand, should be robust to external perturbations but respond with agility to input perturbations from the controller. Dr. Byl outlined an algorithm for reaching optimal performance by first quantifying performance based on a series of actions then designing a policy that optimizes the performance based on the given information. Given a current state and info about upcoming terrain, the robot can use machine learning to develop a policy for the best action to perform from a finite set of choices. One can gain a reduction in dimension by considering only reachable states.

Predicting how people will move using energy optimality: in steady locomotion, in unsteady tasks, in response to external perturbations, and under uncertainty
Manoj Srinivasan (The Ohio State University)
The overarching goal of Dr. Srinivasan's work is to understand human locomotion in order to predict how a persion will move in any novel situation. The hypothesis, based on research over the past few decades, is that humans move in a manner that approximately minimizes energy cost. Dr. Srinivasan presented a series of experiments associated mathematical models that show energy minimization is a good predictor of human behavior in a variety of unconventional tasks: unsteady locomotion with changing speeds, locomotion along a curved line, tasks involving switching between running and walking, etc. In each case, Dr. Srinavasan showed through measurements of cost energy (oxygen consumption) as a function of locomotion parameters that people tend to operate near an optimum.

THURSDAY, NOVEMBER 16, 2017

Gait transitions in a phase oscillator model of an insect central pattern generator
Phil Holmes & Zahra Aminzare (Princeton University)
Legged insects exhibit different gaits; in particular, slow insects tend to use a tetrapod gait, in which two legs are in swing while four remain in stance. In contrast, fast insects employ a tripod gait, with three legs in swing and three in stance. Notably, fruit flies span both of these gaits: they transition from tetrapod to tripod behavior at intermediate speeds. These gaits are partially created by the neural activities of central pattern generators (CPGs), and Dr. Homes and Dr. Aminzare introduce a bursting model for CPG components to study the effect of stepping frequency on such gait transitions. In their model, each cell represents a hemi-segmental thoracic circuit of the CPG.

Under phase reduction, their full bursting model of 24 ordinary differential equations can be reduced to 6 coupled phase oscillators (one for each leg). Assuming that the left and right legs maintain a constant phase difference, Dr. Aminzare showed that these 6 equations could be further reduced to 2 equations. These tractable equations describe the phase differences between the insect's front leg and middle leg, and its hind leg and middle leg, respectively. Conducting a bifurcation analysis of this system and using data fitted to walking fruit flies, they showed that bifurcations occur from stable tetrapod gaits to a unique stable tripod gait as speed increases.

From steady states to transitional tasks
Daniel Koditschek (University of Pennsylvania)
Decades of collaborative work have led to a framework for developing robots with complicated bodies that exhibit robust steady state gaits using combinations of simple controllers. However, Dr.

Koditschek noted that the growing collection of transitional behaviors his lab's robots can perform remains ad hoc. In particular, there is little reuse of modular generators and a common theoretical framework for representing and the desired robot tasks is still lacking. After reviewing some research on steady state gaits, Dr. Koditschek presented examples of some of his robots engaging in interesting transitional tasks. For example, he showed a robot exhibiting a leaping motion using its tail. He also speculated on what an encoding formalism for transitional tasks might entail. In the transitional task setting, appropriate steering of ground reaction forces seems to play a central role, and this suggests that it is important to account for and specify useful consequences of contact conditions.

Automated synthesis of complex movements with large-scale numerical optimization
Emanuel Todorov (University of California San Diego)
The space of possible control laws for a physical system is enormous. Researchers have developed several good classes of control laws, (e.g., sliding mode, passive dynamics, PID, state machine) but these constitute only a small fraction of the available laws. An alternative to using human designed control laws is to instead design optimizers with costs and dynamics and then to allow a computer to actually discover the necessary control laws. These may be laws that humans could not have conceptualized. In his talk, Dr. Todorov talked about several different optimizers that he has developed and demonstrated their performance in both physical simulators and with actual robots.

One of the main challenges for optimizers is enumerating all possible contact sequences. For example, when a human hand rotates an object, the dynamics and forces changes depending on which surfaces of the hand are in contact with the object. Thus, there is a combinatorial explosion in the number of possible contact sequences all of which the optimizer must search over. Dr. Todorov's algorithms use novel continuous methods with contact dynamics to avoid searching over this entire space of contact sequences. He suggested that better controllers can be developed by the combining human insight and controller design with numerical optimization over the space of controllers.

Variational and Robust Optimization of Dynamic Behaviors
Scott Kuindersma (Harvard University)
In his talk, Dr. Kuindersma discussed some of his lab's recent efforts to improve the robustness and accuracy of optimization algorithms for designing dynamic robot motions. Recently, there has been significant interest in contact-implicit trajectory optimization algorithms that remove the need for contact mode pre-specification by optimizing contact forces over time. However, their reliance on first-order dynamic constraints leads to a linear tradeoff between optimization problem size and plan accuracy. Dr. Kuindersma discussed a generalization of existing direct contact-implicit methods that uses ideas from discrete mechanics to derive constraints that achieve higher-order integration accuracy (which has been shown to significantly impact tracking performance). He also also briefly described a robust extension of the classic direct transcription algorithm that reasons about closed-loop responses to disturbances during trajectory optimization.

Using computational fluid dynamics to understand the neuromechanics of jellyfish swimming
Laura Miller (University of North Carolina, Chapel Hill)
Dr. Miller discussed the development and implementation of a model for the pulsation and movement of jellyfish bells. The swimming jellyfish is captured by a nueromechanical model of

the elastic organism interacting with a fluid. It integrates feedback between the conduction of action potentials, the contraction of muscles, the movement of tissues, and fluid motion. Jellyfish are a mathematician's model organism because of their simple morphology and muscular structure. They are ideal for mathematical description due to axisymmetric shape and simple swimming gait consisting of muscle contraction followed by elastic recoil. Dr. Miller considered two classes of jellyfish separately: Oblate jellyfish swimming can be described as paddling the vortex rings expelled during the expansion and recoil of the organism's bell interact strongly with the swimming organism itself. Prolate jellyfish expel the vortex rings much more rapidly to propel themselves forward and there is little interaction. An immersed boundary approach to fluid structure interaction was employed to integrate the model. Discretized Eulerian equations on a Cartesian grid are used for the fluid while discretized Lagrangian equations on curvilinear mesh for are used for the jellyfish. The system was implemented within the existing numerical framework called IBAMR that employs adaptive mesh refinment to solve for velocity, pressure and force.

Simulations from the model indicate that Prolate jellyfish maximize swim speed by forcing in resonance with the free frequency of vibration of the bell. Oblate jellyfish, on the other hand can make use of passive energy recapture since the continue to get pushed forward through interaction with the vortex even after the contraction.

Dynamic force control in static grasps
Satyajit Ambike (Purdue University)
Dr. Ambike discussed a grasping experiment in which subjects were given two tasks: A steady task in which they were asked to put a cross into a target square using input forces from four fingers and a dextrous task in which they were asked to follow a moving square by changing the applied force from the fingers. Unbeknownst to the subjects, there was always a section in the dextrous task where the square remained stationary for a significant amount of time. This allowed for comparison of performance between subjects knew they needed to keep the forces constant and when they were anticipating movement at any time. Analyzing the data within an uncontrolled manifold approach, Dr. Ambike broke the 4D state space composed of the inputs from the four fingers into a 3D linear space (Uncontrolled Manifold) with large variance and a 1D linear space (Orthagonal Variance) with little variance. The main result of the experiment was that the subjects did not reach the same level of stability in maintaining the cross in the square in the dextrous task as they did in the steady task. This might be expected based on the assumption that people prepare for expected change by lowering stability of the current state. The surprising result was that younger adults did not do better than older adults as one might expect. However a closer look at the data shows that younger adults tend to reduce their variance in the uncontrolled manifold in the dextrous task while older adults do not. This may suggest that younger adults are selecting states that are more suitable to change in response to expectation while older adults are unable to do so.

Even more about vision and locomotion
Jonathan Mattis (University of Texas, Austin)
Dr. Mattis presented experimental work to track both foot placement and gaze as humans walk over three different types of terrain: rough, medium and flat. The goal of the study was to examine correlations between where people look and where they step in order to extract information about the underlying control algorithm that can successfully navigate over a variety of terrains. The

main result Dr. Mattis presented was that people tend to look about 2 steps ahead on rough terrain and between 2 and 3 steps ahead on medium terrain. In both cases, this corresponds to approximately where the person will be stepping about 1.5 seconds in the future. The implication is that people tune gaze behavior to the uncertainty of the environment to maintain a strategy of planing foot placement about 1.5 seconds into the future.

Dynamics of hovering, landing and falling in insects, birds and bats: The dynamics of the birds and the insects and the bats
Kenny Breuer (Brown University)
Animals with a ride range of body masses and wing shapes exhibit hovering, forward flight, and aerial maneuvering. While animals with low body mass (such as insects or hummingbirds), buoyed by rigid, lightweight wings, have limited kinematic control, bats exhibit extreme maneuverability. In particular, Dr. Breuer described bats as falling with style (going from flying upright to hanging upside down), a behavior involves using wing inertia to maneuver at low speeds. Unlike insect wings, bat wings are highly articulate and heavy relative to the organism's total body mass.

To study how bats maneuver, Dr. Breuer and his colleagues observed bats flying in an experimental setting and generated virtual images of bat movement by tracking 50+ degrees of freedom (joints). They then generated in silico movies of virtual bats flying. To reduce the degrees of freedom, they used a simple parametrization: wing extension, flapping, pronation/supination, and (x, y, z) position coordinates in space. This led them to simplified equations of motion, and, using these, they found that aerodynamic forces are relatively unimportant to bat maneuverability during reorientation motion at low speeds. On the other hand, hovering motion depends heavily on the ability of bats to change their wing span; it is much more difficult to fly with heavy wings using a constant wing span.

In defense of Aristotle: is there a Connection for multi-legged locomotion?
Shai Revzen (University of Michigan)
When building models of the physical world, it is important to ensure your model is not overly complex and accurate relative to the accuracy of the data you can actually measure; in particular, good models are about simplifying as much as possible, but not more. With this in mind, Dr. Revzen's motivation in his talk was to develop rapid models for simulating the behavior of multi-legged robots. The purpose of these models is to help plan and design better robots; thus, Dr. Revzen noted his models only need to be approximately right, but they must run much faster than real time to be useful. In addition to other systems, he considered a multi-legged robot; observing such a mechapod robot steering and a cockroach steering, he found that both exhibit slipping. The movement of these slow walkers is largely friction-dominated, so he assumed momentum does not matter, friction dominates, and critical velocity is reached immediately. His model inputs are egocentric foot motion, and his parameters are (time-dependent) stiffness and friction. If one makes the assumption that power is the limiting factor and friction is high, critical velocity is reached quickly. Thus, for this system, Dr. Revzen noted that Aristotle was right – "impetus" forces instantly produce their critical velocities.

Robustness, flexibility, and sensitivity in a multifunctional motor control model
Yangyang Wang (Mathematical Biosciences Institute)
How can behavior be both robust and flexible? How is sensory feedback incorporated in the central pattern generator (CPG) to produce robust, flexible behavior? Motivated by these

questions, Dr. Wang's talk focused on studying robustness and flexibility in the specific case of sea slugs (Aplysia). She presented a neuro-mechanical model for Aplysia feeding consisting of 6 ODEs and defined the task fitness to be the total amount of seaweed consumed over the total time of feeding. Using this definition, once can ask how robust the model is to perturbation. Notably, Dr. Wang and her collaborators found that a 40% increase in load caused only a 1% change in task fitness, demonstrating that feeding is robust. She then generalized existing techniques to limit cycle systems with piecewise smooth dynamics and hard boundaries, and used variational analysis to track how the shape of the limit cycle changes under sustained perturbation. Applying their analysis to the Aplysia mdoel, she concluded that sensory feedback mediates robust motor control by changing the shape and timing of neuro-mechanical trajectories.

FRIDAY, NOVEMBER 17, 2017

Learning motor control with many computers and big neural networks
Yuval Tassa (Google DeepMind)
Deep Learning has been applied to discrete problems including Atari and Go, and now these techniques are being applied to motor control (note that "deep" here refers to learning by a multi-layered neural network). As Dr. Tassa described, there are multiple methods for reinforcement learning: value-based methods, in which you are trying to find the action that will maximize future rewards, are the most sample-efficient and are popular in discrete domains (e.g. they were used to solve Atari), but are not often used in control problems. On the other hand, policy-based methods are high-dimensional, used in continuous domains, and widely employed in control; they are robust, but not data-efficient. Finally, though not his focus, Dr. Tassa noted that model-based methods are a third means of reinforcement learning that uses a known/learned differentiable model of system dynamics to improve policy.

After outlining the various methods of reinforcement learning, Dr. Tassa presented some example results of simulated and real robots. One example was a simulated robot developed with data-efficient reinforcement learning for dexterous manipulation. He noted that it was impossible for the robot to learn grabbing when a sparse reward was specified; instead, it is critical to reward shaping and variable initial states. In the same theme of variability being important, Dr. Tassa mentioned that if you train in simulation, you should change the color of the simulation background (because training in simulation is pixel-based) so that the neural network learns what is important and what is not. When such variability is introduced, training in simulation transfers much more readily and robustly to reality. Dr. Tassa concluded his talk by showing a simulated humanoid walking in a different environment than it was trained in. Notably, noisy training led to the humanoids performing well in these new environments.

The unruly actuator: the non-deterministic behavior of skeletal muscles requires fault-tolerant control
Tom Roberts (Brown University)
Muscles do not do what they are told. Instead, they are complex and unruly – muscles are messy actuators. The mechanical outcome of muscle dynamics depends on length, velocity, fatigue, the environment, and other factors. Neuro-motor control contains instructions on the number of muscles cells to depolarize, and the mechanical output of these cells, in turn, depends on acto-myosin behavior, dynamic muscle architecture, the behavior of elastic elements, and the variability of loads and movements with motion. Interested in this variability from the perspective of control,

Dr. Roberts asked if the unruly behavior of muscles is a bug or feature that has evolved. In particular, would motor control be easier or harder and more or less effective if the actuator or muscle was better behaved? As an example, why has natural selection resulted in a springy element in tendons? Elasticity provides some mechanical benefits, but their significant for control remains unclear. Within muscles, elasticity may also be a central determinant of the energetics of contraction. In conclusion, Dr. Roberts noted that his questions about the function of muscle unruliness remain unanswered, but he suggested that these questions provide a useful, insightful way of thinking about muscle dynamics from the standpoint of control.

Modeling molecular-scale muscle activation: why it's important and why it's hard
Sam Walcott (University of California, Davis)
Humans and animals appear to move in ways that minimize their metabolic cost. While being able to predict the metabolic costs of different movements is thus critical to studies of human/animal movement, there are few reliable metabolic cost models available. Motivated by these challenges and noting that the consumption of chemical energy by muscles underlies metabolic cost, Dr. Walcott suggested that we start at the molecular scale and ask what this scale can tell us about larger scales. In particular, a better understanding of muscle contraction at the molecular scale could lead to improved models of muscle energy consumption. Experimental studies in this area have largely focused on understanding the interaction of myosin, which generates force, with actin, a structured protein. This interaction is complex, tightly regulated by additional proteins, and related to local coupling between myosin molecules. In his talk, Dr. Walcott discussed how activation is measured experimentally at the molecular scale and presented some predictive models that describe activation from the molecular to the muscle scale. He found that activation introduces a cost for the rate of force development (because myosin-binding-induced activation is strong but slow), leading to the potential for new metabolic cost models.

Spring Workshop 1 - Host-Pathogen Dynamics (February 19-23, 2018)

Organizers: Carolyn Cho (Merck Research Laboratories), Daniel Coombs (University of British Columbia), Alan Perelson (Los Alamos National Laboratory), Larry Schlesinger (Texas Biomedical Research Institute)

Report by: Amir Asiaee T., Colin Klaus, and Farrah Sadre-Marandi

MONDAY, FEBRUARY 19, 2018

Validating models of influenza-bacterial coinfection
Amber Smith (St. Jude Children's Research Hospital)
Influenza A virus (IAV) infections are often complicated by bacterial pathogens like Streptococcus pneumoniae (SP, pneumococcus), which have accounted for 40-95% of IAV-associated mortality. IAV-SP coinfection is characterized by rapid, uncontrolled bacterial growth, a rebound in viral titers, and a robust inflammatory response. Several factors contribute to influenza-pneumococcal pathogenicity, including aberrant immune responses, tissue destruction, and pathogen strain and dose.

To determine the contribution, regulation, and time-scales of different mechanisms, Dr. Smith and her team analyze infection kinetics with mathematical models then experimentally validate their model predictions. They identify how virus induced alveolar macrophage (AM) depletion dictates bacterial establishment and initial growth kinetics, and that bacteria enhance virus replication efficiency by blocking interferon (IFN) signaling. Although lethality corresponds to the degree of AM depletion, the data indicate that additional mechanisms may contribute to the development of pneumonia in co-infected mice.

To further understand the dynamics of host responses during coinfection, they infected mice with IAV then SP at different times post-influenza. Modeling these data suggests that new infections contribute to the viral rebound while suppressed T cell responses have little impact, and that the increased AM depletion and other immune exacerbations are bacterial mediated. Together, their models and data provide insight into the mechanisms of IAV-SP coinfection, demonstrate the accuracy and predictive power of theoretical models, and highlight the importance of validating model predictions.

Mathematical modeling provides evidence for enhanced clearance of ZIKV infected cells at low challenge doses
Katherine Best (Los Alamos National Laboratory)
Recent Zika outbreak associated with neurological and fetal complications. Most important immune responses to Zika virus is still unclear. Dr. Best first described previous efforts for modeling Zika virus dynamics which have been done with high challenge doses. In high doses, the viral dynamics is fast, and we may miss observing an implicit immune control effect. In her recent work on data collected from monkeys infected with low doses of the virus, she tries to investigate the presence of immune response. For modeling the infection dynamic of the 28 samples infected with two variants of the Zika virus, Dr. Best applies non-linear mixed effects population modeling techniques. Based on the fitted model, she concluded that the inoculum dose has a clear relationship with the increasing death rate of the infected cells which suggests that the immune response is killing the infected cells.

Modeling virus-innate immune interactions: the roles of the spatial and temporal dynamics of interferon signaling
Ruian Ke (North Carolina State University)
The host innate immune response, particularly the type I interferon (IFN) response, is an important determinant of viral replication, viral transmission, and host species range of viral infections. This is underscored by fact that all virus evolved mechanisms to interfere with IFN signaling and also by fact that interferon signaling is highly regulated.

There have been several key quantitative studies of virus-IFN interaction using modeling to explain experimental/clinical observation and estimate key parameters. This talk instead asks how does IFN signaling regulate host cell response to stop viral invasion and how does space affect the modeling? This investigation is conducted using ODE, PDE, and cellular automaton models. The ODE model concludes that IFN does not change infection threshold because in the ODE all cells communicate with another instantaneously. On the other hand, in the PDE model interferon can stop the viral spread where target cells instead become refractory cells. IFN stops virus infection by inducing a layer of protected cells that contain the virus spread but sensitive to ratio of diffusion coefficients between interferon and virus, becoming stochastic when approximately the same.

Belief is that interferon diffuses much faster in vivo owing to its small size. The conclusions are that interferon signaling is most effective when contacts between virus and target are spatially constrained and interferon diffusion is faster than the virus, eg possibly in peripheral tissue. These models show IFN signaling is less effective when contacts are homogeneous, eg possibly an infection in the blood.

Passive vaccination to engineer the germinal centre reaction
Narendra Dixit (Indian Institute of Science)
The speaker and his team explored how administration of passive antibodies can upregulate the antibody response of the germinal center and its implications for vaccination protocols. As antigen availability can also affect the humoral response, key questions addressed were "How do passive antibodies and antigen availability influence the germinal center reaction?" "If you administer passive antibodies, can you then produce antibodies which are more potent in the long run," and "Which passive immunization protocols (affinity of injected antibodies, antigen availability) would yield high affinity antibodies in sufficient amounts?"

Authors found that the simulations of their models do recapitulate experimental observations, that also the affinity of the passive antibody as well as antigen availability tune the germinal center reaction. With their model they were able to predict protocols that maximized the GC output given antigen availability. They found protocols which maximized Day 14 plasma cell output were similar to those that maximized Day 9 output. Very loosely it was found in low, medium, or high availability antigen environments, the introduction of passive antibodies of low, medium, or high affinity performed best. In their talks, authors showed the relative efficacy of all 27 pairings of low, medium, high affinity passive antibodies administered three times for a 9 and 14 Day trial in the presence of varying concentration of available antigen.

Targeting cellular proliferation to achieve HIV cure
Joshua Schiffer (Fred Hutchinson Cancer Research Center)
Need for an HIV cure stems from the need to reduce cost, stigma, toxicity and treatment failure, and to decrease partner to partner transmission. During ART therapy there is a 3 stage decrease in viral load, owing not depleting the virus but the virus factories. Even after decades of ART therapy, if stopped, the virus does eventually return leading to AIDS and death. Measuring the presence of HIV DNA is not a good way to assess quantities of infectious HIV virus because most of that DNA has deleterious mutations. Only .1-10% of that DNA belongs to active replicating virus. There 3 proposed mechanisms of HIV replication that yield reproductive and non-reproductive virus: ongoing replication, longevity, and proliferation. Using phylodynamics, one can measure the accrual of mutations and gather evidence for the three different mechanisms. These three different mechanisms would each lead to their own therapeutic solution.

The authors plan a clinical trial using Mycophenolate mofetil which inhibits the proliferation of B and T lymphocytes. Its hypothesis is that prolonged anti-proliferative therapy for 2 years will lower reservoir volume of HIV DNA and replication competent HIV DNA and replication competent HIV. A reduction in reservoir volume would strongly support the hypothesis that proliferation helps sustain the HIV reservoir. A lack of reduction would not conclusively disprove the hypothesis. There could in that case be other factors including poor drug delivery, or the rate of CD4+ death or daughter cell death may be intertwined with proliferation rate. Not to mention, there are other reasons it might fail after the trial in later stages.

Dynamics of HIV/SIV reaction from latency
Miles Davenport (University of New South Wales)
In HIV treatment, patients with chronic infection go on therapy (ART) where the presence of virus goes even under the detection level. However, once ART is stopped, the virus comes back a few weeks later owing to latent cells. Drugs to get remission are desirable, where disease disappears for a few years not a few days after a stop in treatment. This is a different problem from preventing an initial infection. With primary infection, there are 1-10 virions approximately and trying to block the first infected cell. With reactivation, there may be 5,000 to 50,000 virions though still the need is to block now the first reactivated cell. The questions are what are the determinants of reactivation frequency: for example, are time of initial treatment, duration of treatment, reservoir size, reservoir activation?

The HIV reservoir is sustained by clonal proliferation of infected sites, and anti-proliferative therapy may be an effective way to reduce HIV reservoir volume and achieve functional cure. The authors are interested in estimating frequency of successful HIV reactivation up to detection threshold level. The average frequency was measured as about 1x a week in 4 independent 100 person clinical trials. Another means of assessing success of achieving remission not just to measure the DNA but actually interrupt the ART patients' therapy and see how long till rebound is attained. From this, experimental data suggests that reactivation rate grows surprisingly slow compared to total population of infection. Findings are that time of initial treatment, duration of treatment do affect rebound. However, reservoir size and activation appear to not. Nor does immune activation or immune response. What emerges from these considerations is that the reservoir is established very early. DNA/RNA/activation does not predict reactivation rate. Reactivation may be harder to control than primary infection.

TUESDAY, FEBRUARY 20, 2018

Dengue viral vs. innate immune response
Thomas Hoefer (German Cancer Research Center)
In his presentation, Dr. Hoefer hypothesize that in viral infection, the pathogenic viruses must outpace the innate defense they trigger in order to spread in the host. To study this race, he has developed mathematical models that describe how a susceptible host cell population splits upon virus infection and the ensuing interferon response into infected and protected subpopulations.

He then confronts these models with time-lapse imaging data of dengue virus infection of lung epithelial cells, and show that the rate at which infected cells transition to productive virus replication controls whether the virus will spread. He corroborates this prediction by quantifying replication dynamics in individual cells infected by dengue virus. An attenuated dengue virus mutant that is readily recognized by innate immune sensors differs from wild-type virus by having a long transition to productive replication whereas the replication rate itself is hardly affected. His findings suggest that antiviral drugs that inhibit the formation of replication organelles by dengue virus - and other plus-strand RNA viruses will synergize with the innate immune response of the host.

Ebola viral dynamics in NHPs: Insights into virus pathogenesis and antivirus strategies
Jeremie Guedj (INSERM)

Dr.Guedj discussed his recent contributions to the field of Ebola virus and the evaluation of favipiravir, a nucleotide analog initially approved for severe Influenza in Japan. He promoted advantages of broad-spectrum antiviral drugs and favipiravir specifically. He elaborated on the techniques of viral dynamics used to find a suitable dosing regimen in humans infected with Ebola virus during the last 2014-2015 outbreak and then discussed methods to optimize regimen's efficacy using studies in Non-Human Primates. Lastly, he explained the use of modeling to better understand the roles of the innate and adaptive immune response in the pathogenesis and the clearance of the infection, as well as the potential application of favipiravir to other viral infections.

Viral dynamic modeling to inform HIV cure clinical design strategies
Malidi Ahamadi (Merck & Co., Inc.)
There are hard hurdles in designing a clinical trial for HIV cure. From selecting participants and balancing benefits and risks for an unknown treatment, how do we define endpoints for proof-of-concept studies? Mathematical models could be a viable approach to inform POC studies for HIV cure, though there is a high variability in cited parameter values and a challenge to quantify confidence around parameters. To reduce the number of parameters, a Sobol global sensitivity analysis can be conducted to focus on the sensitive parameters whose total effect is above a 5% cutoff value.

To further examine the sensitive parameters, a *in silico* clinical trial via a virtual population is created, which is a set of simulated parameters and initial conditions reproducing the distribution of measured outcomes. This virtual population can quantify uncertainty of input parameters, simulate response to novel therapy, and identify responders and non-responders to treatment. Integrating knowledge from sensitivity and vertical population permit one to improve the selection of key parameters allowing to inform future HIV clinical trials.

Harnessing 'noise' for cell-fate control
Leor Weinberger (University of California, San Francisco)
There have been filters to remove noise coming from cell cycle (intrinsic) and noise coming from environmental (extrinsic) effects. Though even with these filters there are still intrinsic noise effects that are not well understood that come from stochastic fluctuations in gene expression. This noise is found to drive fate-selection decision in bacteria, stem cells, cancer, and HIV's decision between active replication and latency.

These fluctuations can be harnessed to alter cell fate. For example, there is a class of noise-modulating small molecules that can redirect cell-fate decisions. This talk shows how Tats are sufficient to control HIV fate across diverse biological systems. Also the HIV Rev 'Auto-depletion' feedback attenuates noise to stabilize these fates. Many of these noise-modulating molecules are FDA-approved and may represent a potential therapeutic intervention for HIV latency.

Early thoughts on early infection
Jessica Conway (Pennsylvania State University)
Understanding the events that occur following HIV exposure and plasma viremia is critical to the development of interventions, but these events are difficult to study experimentally. Recent

nonhuman primate (NHP) experiments with SIV from the Keele Lab shed light on the dynamics of early viral replication and development of systemic dissemination following vaginal exposure. Here 15 macaques were exposed to HIV.

The experimental data reveal that prior to dissemination, SIV form foci of local infection in the female genital tract (FGT). Viral variants from multiple viral lineages were found within each focus of infection in the FGT. The authors model these infected cell dynamics in the FGT via a simple continuous time branching process assuming no target cell limitation, using observations of viral variants in foci to validate model predictions. The Chapman-Kolmogorov equation with probability generating functions were used to predict the distribution of offspring belonging to their own viral strains and assessing the probability of extinction.

Co-evolutionary races in a recognition space
Shenshen Wang (University of California Los Angeles)
The author presented a preliminary attempt to describe coevolution of antibody repertoire and rapidly mutating pathogens in a phenotypic space, where square distances define binding affinity and hence the likelihood of recognition. This is a similar technique used by Alan Pearson in his notion of shape space, except it is coarser. This recognition space is dual to the physical space in which B cells process and learn antigen features in many parallel microdomains known as germinal centers; the cumulative output (i.e. memory and plasma cells) from these Darwinian units to circulation in turn collectively drive adaptation of the pathogen. The author presented a coarse-grained model that combines phenotypic evolution and population dynamics in responsively changing environments.

Mathematical models of Ebola and its defective viral particles
Carmen Molina-Paris (University of Leeds)
In this talk the author presented a preliminary work to develop a mathematical model of the intra-cellular replication of Ebola virus in the absence and presence of defective virions. Ebola is a highly pathogenic filovirus, and in general there are no filovirus vaccines approved for human use. The aim is to characterise the specific details of the Ebola virus cycle within a single cell, such as transcription, replication and virus assembly. There are challenges with Ebola, not the least of which is it can only be worked with under biosafety level conditions, BSL-4, the highest there is. The need to study the Ebola replication cycle has led to a mini-genome system for Zaire ebolavirus. This mini-genome is incapable of infecting owing to its lacking the necessary viral proteins. The original genome has been stripped to leave only its replication machinery and swap the rest for a reporter, fluorescing gene.

WEDNESDAY, FEBRUARY 21, 2018

A systems biology approach to uncovering mechanisms governing immune responses during TB infection and applications to treatment
Denise Kirschner (University of Michigan)
Tuberculosis (TB) is an infectious disease, one-third of the world's population is infected with mycobacterium TB and new infections occur at a rate of one per second. A stochastic model is created to capture discrete cellular dynamics via a set of well-described interactions, through a multi-scale modeling approach. The goal is to build a virtual human for study of infectious

diseases, vaccines, drug treatment, drug resistance, host directed therapies, biomarkers, and conduct virtual clinical trials.

Virtual clinical trials are used to test four different regimens during an *in silico* protocol for antibiotic treatment. Both uncertainty and sensitivity analysis are used to determine what factors distinguish different granuloma outcomes. Analysis of the dynamics of suboptimal antibiotic exposure show bacterial populations rebound between doses and there is a high risk of drug resistance development. This study also looked at the variability to expose within and between granulomas and the regions with high risk of resistance in "pockets" where the drug is not getting to. This modeling can help provide a link to infection site that can be used to predict optimal treatment and vaccine protocols.

Investigating within-host heterogeneity within Mycobacterium tuberculosis and Borrelia burgdorferi
Leonid Chindelevitch (Simon Fraser University)
Within-host diversity is highly important, indicating the need for individual treatment outcomes since treatments may change if isolates differ by drug resistance. There is also a capacity for hosts to be co-infected which changes the eco-epidemiology of pathogens, pathogen competition/cooperation, or projected impacts of interventions. Thus being able to detect and quantify within-host diversity and whole-genome sequencing methodologies can help us do that. These genotyping methods can detect novel strains automatically or semi-automatically from the data, explore cooperation and competition between strains within the host, and explore the implications for immune dynamics and treatment outcomes.

A 'disease space' network approach to modelling the within-host dynamics of malaria infection
Nicole Mideo (University of Toronto)
Dr. Mideo talk focused on approaches developed by his group to better capture the driving signals of host immunity against early malaria infection. Modeling immunity against malaria parasites is challenging because mechanistic details of immune dynamics are often difficult to quantify, especially at granular levels of detail. Thus, existing models of within-host dynamics of early blood-stage malaria infection often forgo the functional complexity of immune systems, either by modeling immune killing as a variation on simple predator-prey models or phenomenologically as a clearance rate over time.

He described immune responses as functions of multivariate phenotypic space: namely, the density of resources (red blood cells) and parasites. To allow for functional flexibility in response to within-host conditions, the immune system is conceptualized as a network, where nodes represent anything from a single protein to entire modules of proteins and signal-transduction pathways. Empirical data was used to optimize and generate a minimal adequate immune network, which amounts to a simple analytical description of host immune regulation in response to the changing within-host environment during infection. By predicting immune activity through the disease space, presented systems approach holds promise for connecting the outcome of infection to immune responses.

Infection in space: Quantifying viral transmission dynamics dependent on the tissue structure
Frederik Graw (Heidelberg University)

Several pathogenic viruses are capable of spreading within a host by two different modes of transmission, i.e., cell-free and cell-to-cell spread. To which extent these viruses, such as hepatitis C virus (HCV) or human immunodeficiency virus (HIV), spread by each of the transmission modes, and how target cell tropism and tissue structure affect the transmission dynamics, has not been determined so far. Mathematical models are essential to provide a systematic and quantitative understanding of viral infection dynamics. However, previous models mostly ignored the spatial structure of the target cell population and insufficiently accounted for cell-to-cell transmission.

Dr. Graw presented novel mathematical models developed by his team to quantify viral transmission dynamics dependent on target cell morphology and tissue structure. These models include extended population dynamics approaches based on bulk measurements of viral concentrations and infected cells, as well as spatially explicit agent-based models following individual cells and their interactions. He showed that applying these models to experimental data on the spread of HCV and HIV in vitro, provides insights into the interplay of cell-free and cell-to-cell transmissions. The suggested analyses allow a more reliable quantification of viral transmission kinetics for different tissue conditions. Quantifying these kinetics is an important prerequisite to infer the contribution of each of the transmission modes to viral spread and, thus, to elucidate their influence on disease progression.

Modeling the impact of coinfection on persistence and infectivity of P. falciparum malaria
Lauren Childs (Virginia Polytechnic Institute and State University)
Dr. Childs presented a discrete model of blood-stage parasite dynamics including innate and adaptive immune responses for malaria developed to explain malaria's specific behavior. One of the most notable features of malaria is the variable course and duration of infection experienced by different individuals, ranging from high parasite density, acute and often severe infections to persistent, chronic infections that are often undetectable by microscopy. Field studies examining persistence of infection have used a variety of different genotyping methods, but due to limitations, it is difficult to determine the extent of mixed infections, and nearly impossible to determine if the reemergence of parasitemia is due to a new infection or recrudescence of an existing one.

Mathematical models, despite limited knowledge of mechanistic details of host-parasite interactions, have qualitatively reproduced single parasite dynamics observed in patient data. Dr. Childs analyzed the simulated output of her suggested model and examined how coinfecting strains, particularly from similar clones that elicit overlapping immune responses, impact infection length and infectiousness. She found that the level of both innate and adaptive immune responses present at the time of coinfection as well as the similarity of the coinfecting strains significantly alters the duration of both the resident and coinfecting strains, particularly during chronic infections. Also, timing of coinfection influences the infectivity of the coinfecting strains, likely altering transmission patterns at a population level.

Life cycle synchronization is a viral drug resistance mechanism
Alison Hill (Harvard University)
HIV can be effectively treated and prevented with antiretroviral therapy, but the evolution of drug resistance can cause treatment failure. Antiviral drugs typically target a specific phase of the virus's life cycle, and it is generally assumed that resistance arises from mutations that alter the virus's susceptibility to the direct action of the drug. Here the author considers the alternative possibility that a virus population can evolve towards synchronizing its life cycle with the pattern of drug

therapy. The periodicity of the drug treatment could then allow for a virus strain whose life cycle length is a multiple of the dosing interval to replicate only when the concentration of the drug is lowest. This process, referred to as ``cryptic resistance'', could allow the virus population to maximize its overall fitness without having to alter drug binding or complete its life cycle in the drug's presence.

An analytical expression for viral fitness that is sufficient to explain the drug-pattern-dependent survival of strains with any life cycle length was discussed. A new analytical expression for R_0 that accounts for a synchronization is obtained. The implications of these findings for clinically-relevant antiviral strategies for HIV as well as other viruses including hepatitis B and C and influenza were discussed. It is a challenge to diagnose these patterns in clinical data, because the full genome data would be needed to encode the life cycle and phenotypic data is only obtained where constant drug levels are administered. Instead that would need to be periodically done.

Modeling immune escape in intro-host HIV and CTL networks
Cameron Browne (University of Louisiana at Lafayette)
There is an array of CTL immune response populations during HIV infection. CTL populations recognize the viral proteins called epitopes, kill infected cell and proliferate clones. Efficacy and breadth of CTL drive HIV quasispecies evolution. Immunodominance hierarchy is a main determinant in viral escape from multiple epitopes. Thus, understanding complex HIV-CTL dynamics and evolution is important for designing vaccine/immunotherapy.

This talk considers models for the diverse virus “quasispecies” and immune response variant networks, built through viral resistance mutations at multiple epitopes. Results suggest that immunodominance hierarchy has a larger effect than viral fitness on the escape pathway. Though under uniform mutational fitness costs, the system of 2^n virus strains converges to a perfectly nested network with less than or equal to n+1 persistent virus strains.

Dynamics of lentiviral infection in vivo in the absence of adaptive immune responses
Elissa Schwartz (Washington State University)
Equine Infectious Anemia Virus (EIAV) establishes a chronic persistent infection which has multiple similarities to HIV. Understanding the dynamics of acute viral infection is crucial for developing strategies to prevent and control infection. The goal of this work is to estimate the kinetics of EIAV infection in vivo without immune responses and to quantify the effect of neutralizing antibodies in preventing infection.

The rates of infection, virus production, virus clearance, and infected cell death are estimated. These estimates are then used to calculated the basic reproduction number, virus doubling time, exponential growth rate, and steady state levels of uninfected cells, infected cells, and virus. The leveling off of virus replication in EIAV-infected SCID houses implies that factors other than adaptive immune responses limit the viral growth, such as target cell limitation and/or innate immune response. It was found that the rate of antibodies that neutralized the virus was 17.8 times greater than the virus clearance rate. The minimal efficacy of infused antibodies that successfully prevented infection may be useful in the development of therapies and vaccines.

THURSDAY, FEBRUARY 22, 2018

The persistence of immunological memory
Rustom Antia (Emory University)
The immune system has a long-lasting immunological memory which underlies our current vaccination system. The question is how long immunity is maintained over time in both individual and population level. It is challenging to answer this question for human subjects due to lack of longitudinal data. An interesting data set was collected over 20 – 30 years at Oregon National Primate Research Center for annual health checkups of the staff and was used to measure serum antibodies of 45 individuals. Dr. Anita presented a new deeper analysis of this data set.

He observed that there is a huge difference in vaccine and virus antigen effects. The variation of memory over different individual subjects is small. He concluded with an interesting observation which may help to design a more effective immunization regimen. The study shows that long-term immunological memory at population level happens in two cases: when the initial response has high value or if the decay rate is small.

Mathematical models of dengue virus infections
Stanca Ciupe (Virginia Tech)
Within-host dengue virus dynamics differ between primary and secondary infections, with secondary infections with a different serotype inducing more severe disease. To better understand the mechanistic interactions leading to increased disease severity, Dr. Ciupe and her group developed within-host models of dengue infections. They found that cross-reactive immune responses as described by original antigenic sin (rather than antibody dependent enhancement) may be responsible for disease enhancement. In the next step, they coupled the within-host virus dynamics to a population-level model and examined the between-host infections in the presence of two circulating virus strains that create mild or severe individual infections. Finally using the developed model, Dr. Ciupe derived an analytical threshold for the disease persistence in the population.

Modeling immunological pre-adaptation of HIV-1
Rob de Boer (Utrecht University)
It has been suggested that HIV-1 has evolved its set-point virus load to be optimized for transmission. Previous epidemiological models and studies into the heritability of set-point virus load confirm that this mode of adaptation within the human population is feasible. However, during the many cycles of replication between infection of a host and transmission to the next host, HIV-1 is under selection for escape from immune responses, and not the transmission. Through mathematical modeling, Dr. Boer investigates how these two levels of selection, within-host, and between-host, are intertwined. He finds that when the rate of immune escape in the suggested model is comparable to what has been observed in patients, immune selection within hosts is dominant over selection for transmission. Surprisingly, he finds high values for set-point virus load heritability, and argues that high heritability estimates can be caused by the 'footprints' left by differing hosts' immune systems on the virus.

Environmental influences on T cell motion in intact tissues
Judy Cannon (University of New Mexico)
In this presentation, Dr. Cannon summarized her lab's efforts for determining the environmental influences that can drive the patterns of T cell motion in intact tissues. T cells are a key effector cell type in the immune response, participating in clearing infection as well as in anti-tumor

responses. T cells are able to move through multiple peripheral tissues: naïve T cells migrate in and out of lymph nodes searching for antigen on dendritic cells, while activated T cells migrate to infected peripheral tissues to clear infection. However, as individual tissues differ dramatically in cellular composition and structure, Dr. Cannon hypothesizes that T cells utilize environmental cues within each different tissue compartment to mediate different motility patterns.

By visualizing T cell motion in both lymph nodes and lung, they observe the T cell behavior in relation to native environments. Using a combination of two photon microscopy and computational analyses, they show that T cells in both lymph nodes and lung use environmental structures to set motility patterns. In lymph nodes, a mutual information (MI) metric is used to demonstrate that High Endothelial Venules (HEVs) are responsible for T cell positioning. Surprisingly, the target of the T cell search, dendritic cells, appear not to share MI with T cells. In inflamed lung, they find that effector T cells move with an intermittent motion, with cells going through periods of directional and confined motion. Using novel quantitative tools, Dr. Cannon and her collaborators demonstrate that T cells in lung also move following the vasculature. These data show that T cell motion is influenced by specific environmental components within individual tissues including vessels, suggesting that the context in which T cells move is an important determinant of T cell behavior in vivo.

Modeling Pharmacodynamics on HIV Latent Infection
Naveen Vaidya (San Diego State University)
Highly active antiretroviral therapy has successfully controlled HIV replication in many patients. Yet, the pharmacodynamics characteristics of drugs and the dosing schedule can significantly affect the outcome of either early or late treatment. A mathematical model of HIV latent infection dynamics is presented that integrates the effects of drug pharmacodynamics. The slope of the dose-response curve, the ratio of the maximum dosage to the 50% inhibitory concentration, the drug's half-life and the dosing interval are studied. Variations in each of these parameters can generate either an infection-free steady state or persistent infections when the other parameters are unchanged. A viral invasion threshold is formulated to governs the global stability of the infection-free steady state and the viral persistence criteria.

Multistage models in HIV infection and treatment
Libin Rong (University of Florida)
The HIV life cycle exhibits multiple-stages that includes budding and fusion, reverse transcription, integration, transcription and translation, assembly and budding. These stages may be targeted for interruption by drugs. The author introduced a very general ODE model that was able to reproduce several observations in the literature, concerning a multiphasic decline in viral load exhibited by the RAL, EFV, and other drug interventions.

The author determined that multi-stage models provide a systematic comparison of the effects of different drugs, that drugs acting later in the viral life cycle do not imply higher effectiveness. There are three phases of HIV decline under RAL-contained therapy. In virally suppressed patients, treatment intensification with RAL may not increase 2-LTR or further reduce the viral load. Other treatment strategies such as latency reversion have to be developed for the cure or functional control of the infection.

Modeling infection with delay-differential equations

Jacques Belair (University of Montreal)
This talk surveyed several applications of delay-differential equations to various infections at several different scale levels though not at once. In applications to Hematopoiesis, Erythropoiesis, and Leukopoiesis, the author wanted to compare same class of models to describe production but in context of wanting to control neutrophil. The objective was to develop a mathematical model of blood production system (haematopoiesis) appending administration of chemotherapeutic drug and supporting medication (G-CSF) to determine optimal dosing practices to mitigate myelosuppressive effects of the drug, reduce treatment cost and limit amplitude of oscillations in neutrophil counts (mainly raising lowest ANC). The model was compared to clinical trial data for optimization purposes to minimize neutrophil production. The first trial considered treatment of lymphoma involving concomitant administration of cyclophosphamide, doxorubicin, vincristine and prednisone over 21-day cycles, with G-CSF *ad libitum* adjusted to individual patients. A second trial 10-day duration trial considered G-CSF administration adjusted for patient's body weight, beginning 4 days post-chemotherapy.

FRIDAY, FEBRUARY 23, 2018

Circadian rhythms and host defenses: Is there a role in infections?
Ioannis Androulakis (Rutgers University)
The circadian timing system (CTS) is a vast, hierarchical collection of interconnected, mutually and tightly regulated biological clocks that maintain accurate periodicity of behavioral, biochemical, metabolic, neuroendocrine, immune and physiological functions. The endogenous clock anticipated daily fluctuation in the external environment to maximize physiological fitness. During the active/feeding phase, the encounter with pathogens is more likely and the clock is ready to anticipate the treat by optimizing the immune response. Susceptibility to infections in higher at the beginning of the resting phase and the inflammation levels are massively increased.

Variation in the incidence of many infectious diseases may be due to changes in susceptibility of human host. This hypothesis would predict the pathogens do not physically migrate across the equator and the nationwide epidemics do not necessarily result from chains of person-to-person transmission. Rather, the pathogens may be present in the population year-round, and epidemics occur when the susceptibility of the population increases enough to sustain them.

Impact of modeling and simulation in development of telaprevir
Brian Hare (Vertex Pharmaceuticals)
Systems biology is used to identify the best point to intervene and find combination of targets in a disease to maximize efficacy. The goal is to identify the level and duration of target engagement needed to generate a meaningful response by identifying desirable PK profiles and dose schedules. Additionally, modeling allows for estimates of the probability for a drug to succeed by identifying responsive patient populations and predict outcome in unstudied populations.

This talk discusses the development of the model and impacts on the clinical development of telaprevir, a drug that targets an essential hepatitis C virus protease. The model is integrative and mechanistic, integrating in vitro virology data, pharmacokinetics, and viral response to a combination regimen of telaprevir and peginterferon alfa-2a/ribavirin (PR) in patients with genotype 1 chronic hepatitis C. The model was used to predict the optimal treatment duration and dosing, supporting a 12-week duration for telaprevir of 750 mg q8h dosing as well as response-

guided therapy. The model is also used to estimate the impact of missed doses. Treatment predictions were validated through human trials.

Modeling in the development of Letermovir (LET), for prophylaxis of CMV following allogeneic hematopoietic stem cell transplantation (HSCT)
Carolyn Cho (Merck Research Laboratories)
Prevention of CMV infection in HSCT is an unmet medical need. Current anti-CMV agents are myelotoxic which prevents their use in HSCT recipients. LET inhibits CMV through a novel mechanism involving viral terminus complex. A model is built on nonlinear mixed effects of steady state data. Additionally a multiple dose study is conducted to explain the differences in blood concentration found between Japanese and non-Japanese subjects. Retrospective analysis is performed to determine if dose adjustment is required in Asians or in Asians carrying the minor allele of genes associated with change in PK. The margin for safety and tolerability was discuss as the upper bound of exposure. It was found that LET is highly efficacious in preventing clinically significant CMV infection though Week 24 post-transplant with a ~33% relative risk reduction in mortality compared to placebo.

Drug and disease modeling in development of a new anti-viral treatment for HCMV
Kevin Dykstra (qPharmetra)
The talk began by surveying the uses of pharmacological models in industry. Those uses extend to optimal dosing schedule, optimal trial design, new dosage form, helping to decide whether to proceed or stop development and product position. More technically it is used in pharmacometric models PK/PopPK, PK/PD, Mechanistic Models, Virtual Clinical Trials, Model Based Meta Analysis, and clinical utility. Another big compulsion for modeling in industry is that the FDA requires that modeling be performed. 99% of NDA submissions include pharmacometric analysis.

Specific modeling in this talk focused on human cytomegalovirus (HCMV) which is a member of the Herpes family of viruses. It is generally harmless except to people with compromised immune function. The model is a system of ODE's which accounts for 5 state variables and has 15 parameters. Their model showed that changing the latency parameter had no effect on viral load or infected cells. This observation practically led to reducing the size of the state space from 5 to 3 dimensions with only 8 parameters.

Spring Workshop 2 - Socioepidemiology (March 5-9, 2018)

Organizers: Carlos Castillo-Chavez (Arizona State University), John Drake (University of Georgia), Sebastian Funk (London School of Hygiene and Tropical Medicine), and Eben Kenah (The Ohio State University)

Report by: Colby Long, Inom Mirzaev, and Alexandria Volkening

MONDAY, MARCH 5, 2018

Pairwise survival analysis: Contact intervals, regression, and phylogenetics
Eben Kenah (The Ohio State University)

When integrating epidemiologic data with pathogen phylogenetics, the likelihood for the transmission model is often a branching-process likelihood based on a generation interval distribution. In his talk, Dr. Kenah showed that a misspecificed likelihood can lead to severely biased estimates with or without a pathogen phylogeny. Writing the likelihood as a survival likelihood with failure times in pairs---a method called pairwise survival analysis---accounts for time spent at risk of infection. In a simple example with three infections, Dr. Kenah showed that a pairwise survival likelihood produces more accurate source attribution.

In a mass-action model with negligible depletion of susceptibles, the pairwise survival likelihood depends only on information about infected individuals in the limit of a large population. However, this asymptotic likelihood has cumulative hazard terms that have no counterpart in a branching process likelihood. As an example of the flexibility of pairwise survival analysis, Dr. Kenah described a pairwise accelerated failure time model that can be used to estimate covariate effects on infectiousness and susceptibility. This model—modified to account for the buildup of immunity—was used to estimate the efficacy of the Ebola vaccine based on the WHO ring vaccination trial in Guinea. This trial collected data on individuals exposed to infection who escaped as well as Ebola virus genetic sequences.

Harnessing big data to quantify the spatial and temporal dynamics of vaccine hesitancy behavior

Shweta Bansal (Georgetown University)

Dr. Bansal reported her work on using large scale patient provider interactions data to understand how social behavior and population structure shape infectious disease transmission. In high-income countries, such as the United States (US), coverage rates for vaccination against vaccine-preventable childhood infections remain high. However, the phenomenon of vaccine hesitancy makes maintenance of herd immunity difficult, impeding global disease eradication efforts. Reaching the 'last mile' will require early detection of vaccine refusal (due to philosophical or religious choice), identifying pockets of susceptibility created by underimmunization (due to vaccine unavailability, costs, ineligibility), and determining the factors associated with the behaviors to target strategies to ameliorate the concerns. Towards this goal, Dr. Bansal's group harnessed high-resolution medical claims data to geographically localize vaccine refusal and underimmunization in the US. To process such a large-scale data, Dr. Bansal used a hierarchical Bayesian model. The data source included 86 million patient provider interactions/year, and thus represented the first large-scale effort for vaccination behavior surveillance. Her work has the potential to aid in the development of targeted public health strategies for optimizing vaccine uptake globally in high-income settings.

Data bias at the inference of disease and behavior. Wachoo lookin' at?

Nita Bharti (The Pennsylvania State University)

In this talk, Dr. Bharti talked about her work on examining the underlying mechanisms for spatial heterogeneities in host disease burden and risk across spatial scales and across borders by assessing regional variations in movement and contact patterns relating to outbreaks and access to health care. In low-income settings, vaccination campaigns supplement routine immunization but often fail to achieve coverage goals due to uncertainty about target population size and distribution. Accurate, updated estimates of target populations are rare but critical; short-term fluctuations can greatly impact population size and susceptibility. Dr. Bharti and her collaborators use satellite imagery to quantify population fluctuations and the coverage achieved by a measles

outbreak response vaccination campaign in urban Niger and compare campaign estimates to measurements from a post-campaign survey. Their results indicate that vaccine coverage was overestimated because the campaign underestimated resident numbers and seasonal migration further increased the target population. Therefore, Dr. Bharti and her collaborators combine satellite-derived measurements of fluctuations in population distribution with high-resolution measles case reports to develop a dynamic model that illustrates the potential improvement in vaccination campaign coverage if planners account for predictable population fluctuations.

Ecology of Poverty, Disease and Health Care Delivery: Lessons for Planetary Health
Matthew Bonds (Harvard Medical School)
Over the past two decades, the global health agenda has increasingly embraced the concept of sustainable development in pursuit of solutions at the "systems" level. A central challenge is that the relevant social, economic, and biophysical systems that influence human health and wellbeing operate at difference spatial and temporal scales and scopes of problem solving. In his talk, Dr. Bonds explored three interconnected self-reinforcing systems of central importance to planetary health: the ecology of poverty, the ecology of disease, and systems of health care delivery. He framed these issues to inform how practical interventions can be implemented and studied to create practical systems-level change at the ground level, and establish methods for evaluating that change and producing transferable knowledge for scaling or replication.

Modeling Endemic Foot-and-mouth Disease Transmission
Laura Pomeroy (The Ohio State University)
Foot and mouth disease is a viral disease that negatively affects livestock and hence many local economies in the developing world. In her talk, Dr. Pomeroy talked about her work studying foot-and-mouth disease in the far north region of Cameroon. The objective of her work was to quantify the endemic FMD (foot-and-mouth disease virus) virus dynamics and to determine the best method of control. In order to do this, members of her lab surveyed cattle to document the extent of seroprevalance, quantified the duration of the antibody response in cattle, and attempted to quantify the transmission dynamics.
Dr. Pomeroy and her team were particularly interested in modeling the impact of mobile pastoralists in FMD transmission. To do this, they developed an agent-based model coupled with a traditional SIR (susceptible-infected-recovered) model. Because the pastoralists move their livestock between rainy and dry seasons, they first used data to develop mobility rules for the agents in the model. The simulation results demonstrated that the herd mobility significantly influenced the dynamics of FMD.

TUESDAY, MARCH 6, 2018

Challenges and Opportunities in Theoretical Epidemiology
Carlos Castillo-Chavez (Arizona State University)
The field of modern epidemiology began with the work of Ronald Ross, who won the Nobel Prize in 1902 for his pioneering research on malaria. Dr. Castillo-Chavez began his talk by discussing Ross's work and a broad range of other past and current work on the spread of diseases. He then described how important it is to account for the interplay of human behavior with disease spread, and gave several examples of various types of behavior he models in his research. For example, he mentioned how accounting for behavior in a model of leprosy produced aggregates of diseased and disease-free individuals into distinct communities. As another example, he noted that the evolution

and behavior of influenza epidemics in the US depends on travel patterns: in this way, human travel alters the immunology of a "super-organism" (the whole US). In his models, he found that most secondary cases of influenza take place in homes, not schools; this may be because people take more precautions in schools than homes, and they may miss school when they are sick. In conclusion, humans make decisions on how to respond to the presence of disease risks based on their priorities and needs. This coupling of human behavior and diseases is what makes the study of epidemics a complex and challenging problem.

Correlation equations, US elections, and modeling SIR-epidemics on dynamic random graphs
Grzegorz Rempala (The Ohio State University)
A range of contact-type diseases, including HIV and Ebola, as well as spreading memes or sentiments, such as political opinions, can be modeled as epidemics using the SIR framework. Stochastic SIR epidemic processes on random graphs are a particular class of interaction networks, and they that have become of wide interest for modeling many contact-type epidemics. In this setting, S refers to susceptible individuals, I to infected, and R to recovered. As motivation for his work, Dr. Rempala mentioned that heterogeneous networks are present in both Ebola spread and US political opinion dynamics. The classical SIR differential equations by Kermack and McKendrick (1927) can be seen as a limit of an underlying stochastic process. Dr. Rempala presented his work on an SIR epidemic evolving on a configuration model graph (a random graph initialized with a given degree distribution). Notably, his model allows for connections to be added or dropped in his network in response to infection; this model, which he refers to as SIdR, can be seen as accounting for human responses to the presence of an epidemic. His work yields a law of large numbers for this SIdR process. This enables the development of "network-free" SIdR Markov hybrid models, which lend themselves to the inference of important parameters involved in epidemics.

Epidemic Growth Scaling: Implications for Disease Forecasting and Estimation of the Reproduction Number
Gerardo Chowell (Georgia State University)
Because mathematical models are being used more and more often as tools for forecasting epidemics, it is becoming increasingly important to develop models that are able to reliably capture the baseline transmission features of given pathogens and social contexts. Interested in the role of scaling in epidemic growth, Dr. Chowell began his talk by defining the basic reproduction number, which is the number of secondary cases generated by a primary infectious individual during the early phase of an epidemic outbreak (in an entirely susceptible population). Major epidemics can occur when the reproduction number is larger than 1; mathematically, the reproduction number is linked to the idea of exponential growth of epidemics. As Dr. Chowell discussed, however, data from empirical outbreaks shows a range of different epidemic growth patterns; in particular, epidemic growth is not always exponential. The scaling of growth is impacted by many factors, including human behavior (e.g. human reactions to the presence of an epidemic), heterogeneous susceptibility, and spatial effects. Dr. Chowell discussed recent progress on modeling and describing the initial spread of epidemics using infectious disease outbreak data. His work shows that incorporating human heterogeneity into mathematical models supports sub-exponential epidemic growth, while removing this heterogeneity recovers exponential growth behavior.

Where the wild things are: the impact of time reallocation on the cost and benefit of school closures during an epidemic

Eli Fenichel (Yale)
In this talk, Dr. Fenichel reported his recent investigation on the impact of school closure days on the spread of epidemics. School closures are an important public health intervention during epidemics. Yet, the existing estimates of policy costs and benefits overlook the impact of human behavior and labor market conditions. Dr. Fenichel modeled and quantified the public health benefits and the economic costs of school closures based on activity patterns derived from the American Time-Use Survey (ATUS). Furthermore, he developed a policy decision framework based on marginal benefits and costs to estimate the optimal school closure duration.

The results of the developed framework suggest that an 18-day nationwide school closure is optimal in the US when implemented during a pandemic influenza approximately twice as severe as H1N1 (swine flu). In addition, the closure could cost between $14 and $18 billion and avert 26 to 37 million cases depending on the behavior of the population. Finally, these models show that the ability to work from home, particularly in higher paying jobs, may increase public health benefits and reduce the economic burden of school closures.

Activity patterns and ecological networks: identifying shared exposures to social contexts
Catherine Calder (The Ohio State University)
In the social and health sciences, research on 'neighborhood effects' focuses on linking features of social contexts or exposures to health, educational, and criminological outcomes. Traditionally, individuals are assigned a specific neighborhood, frequently operationalized by the census tract of residence, which may not contain the locations of routine activities. In order to better characterize the many social contexts to which individuals are exposed as a result of the spatially-distributed locations of their routine activities and to understand the consequences of these socio-spatial exposures, Dr. Calder and her collaborators have developed the concept of ecological networks. Ecological networks are two-mode networks that indirectly link individuals through the spatial overlap in their routine activities.

In this presentation, Dr. Calder focused on statistical methodology for understanding and comparing the structure ecological network(s). In particular, she proposes a continuous latent space (CLS) model that allows for third-order dependence patterns in the interactions between individuals and the places they visit and a parsimonious non-Euclidean CLS model that facilitates extensions to multi-level modeling. Finally, she illustrated their methodology using activity pattern and sample survey data from Los Angeles, CA and Columbus, OH.

WEDNESDAY, MARCH 6, 2018

Behavior, Learning, and Outcomes in Epidemics
John Drake (University of Georgia)
The standard assumption of SIR (susceptible-infected-recovered) models is that an outbreak ends when the removal rate exceeds the transmission rate. In these models, the removal rate typically decreases due to susceptible depletion and vaccination. However, in his talk, Dr. Drake argued that very few outbreaks actually fit this standard model. As a recurring example throughout his talk, he used data from an outbreak of SARS in Toronto from 2003. The scale of the outbreak was such that susceptible depletion was not an issue and no vaccine was developed. Instead, the outbreak ended due to the onset of interventions such as patient isolation, contact tracing, and social distancing.

Dr. Drake argued that in order to understand these outbreaks, we need a theory of outbreaks with interventions that take into account societal learning. For example, as an outbreak progresses, the apparatus for identifying and isolating infected individuals improves in efficiency and the removal rate of infecteds increases. As he explained, studied in this way, we can study the distribution of outbreak sizes and trajectories to determine the effectiveness of different containment strategies. He concluded his talk with two open questions related to modeling outbreaks with interventions. One, how affective are interventions in the face of more complex disease transmission processes (e.g., latency periods, multiple transmission pathways)? And two, what are the limits to achieving the maximum removal rate?

Human behavior and the global spread of vector-borne pathogens
Michael Johansson (Centers for Disease Control and Prevention)
The recent pandemics of chikungunya and Zika highlight the challenges posed by arboviruses in an interconnected world. In his talk, Dr. Johansson discussed how models provide important insights into the risk of international spread of these viruses. Infection risk for travelers depends on prevention measures, where travelers go, where they stay, and how long they stay for, all of which influence the risk of international spread. The risk of transmission in places receiving infected travelers also depends on human behavior because exposure to competent mosquito vectors is requisite for onward transmission.
For tropical locations, heterogeneous individual behavior generally has little impact on population-level risk of introduced transmission. However, in regions where transmission of these pathogens is rare (e.g. the southern United States) or at times when there are few introductions, individual behavior is likely to play a particularly important role and is not well characterized. Dr. Johansson concluded his talk by emphasizing the need to develop new models to better characterize transmission risk at these margins and guide effective prevention and control strategies.

Dynamics of Multi-host and Multi-vector Models
Derdei Bichara (California State University Fullerton)
Zoonoses are infectious diseases caused by pathogens that are transmissible from vertebrate animals to humans under natural conditions. Crucially, they account for 75% of emerging infectious diseases and, depending on the pathogen, they can be transmitted in a variety of ways: for example, Lyme disease has vector-borne transmission, Anthrax is transmitted indirectly, and Salmonellosis is spread orally or through food. In his talk, Dr. Bichara focused on describing vector-borne zoonoses and analyzing his models. He first considered a general host vector SEIR-SEI model in which a host's infectious state is subdivided into n classes, where each class has a different infection response to the vector. His work suggests that host heterogeneity supports the spread of infection, thus feeding into a so-called "amplification effect."

Furthermore, the results of his analysis reinforce the concept of One Health, in which human, animal, and ecosystem health are seen as interconnected ecologically. He then extended his models to a multi-host, multi-stage, multi-vector epidemic: this describes the evolution of zoonoses where the pathogen is shared by multiple host species and transmission occurs through the biting or landing of an arthropod vector. In addition to other analyses of this model, he computed the basic reproduction number of the system.

Role of vaccination in determining the critical community size for stochastic extinction
Joel Miller (Institute for Disease Modeling)
A recent localized outbreak of CVDPV-2 (circulating vaccine-derived Polio virus 2) in Syria caused great concern for the ongoing effort to eradicate Polio. Over 70 children experienced symptoms in a relatively localized geographic region. Given the fact that fewer than 1 in 1000 infected children would be expected to experience symptoms, this suggests a very high attack rate in the region. No cases have been identified since September, and there is (as yet) no evidence that it has spread from the region.
In his talk, Dr. Miller presented a plausible explanation for the presence and disappearance of this outbreak: that lack of vaccination in the region led to a large outbreak which then went extinct, hopefully without seeding other regions. This leads to the possibility that there may be two modes for extinction in a sufficiently isolated community: either high vaccination leading to high immunity, or a large epidemic leading to high immunity. It is plausible that there is an intermediate regime where insufficient vaccination coverage leads to persistence within a community. Dr. Miller presented some preliminary work in which he explored this possibility using some simulations and analytic models.

Ecology of Poverty and Disease: A coupled systems approach
Calistus Ngonghala (University of Florida)
The rural poor generally rely on their immediate natural environment for subsistence and suffer from high burdens of infectious diseases. In his talk, Dr. Ngonghala presented a general framework for modeling the ecology of rural poverty, focusing on the exemplar drivers: infectious diseases, renewable resources, and land-use change. Interactions between these drivers and economics create reinforcing feedbacks resulting in three possible development regimes corresponding to globally stable wealthy/healthy development, globally stable unwealthy/unhealthy development, and bistability. He showed that the proportion of parameters leading to poverty is larger than that resulting in healthy/wealthy development, that bistability consistently emerges as a general property of generalized disease-economic systems, and that the systems under consideration are most sensitive to human disease parameters. The framework highlights feedbacks, processes and parameters that are important to measure in future studies of development in order to identify effective and sustainable pathways out of poverty.

THURSDAY, MARCH 7, 2018

How stochasticity influences leading indicators of critical transitions
Suzanne O'Regan (North Carolina A&T State University)
Many complex systems exhibit critical transitions. Of considerable interest are bifurcations, small smooth changes in underlying drivers that produce abrupt shifts in system state. Before reaching the bifurcation point, the system gradually loses stability ('critical slowing down'). Signals of critical slowing down may be detected through measurement of summary statistics, but how extrinsic and intrinsic noise influence statistical patterns prior to a transition is unclear.

Dr. O'Regan considered a range of one-dimensional stochastic models that exhibit transcritical, saddle-node and pitchfork bifurcations. Noise was assumed to be either intrinsic or extrinsic. She derived expressions for the stationary variance, autocorrelation and power spectrum for all cases. Trends in summary statistics signaling the approach of each bifurcation depend on the form of noise. For example, models with intrinsic stochasticity may predict an increase in, or a decline in

variance as the bifurcation parameter changes, whereas models with extrinsic noise applied additively predict an increase in variance. To examine how noise influences spatially extended systems, Dr. O'Regan additionally developed spatially implicit two-patch models with additive and multiplicative forms of environmental stochasticity that are slowly forced through population collapse and through changing environmental conditions. Finally, she showed that the noise regime and the degree of coupling together determine trends in summary statistics. She concluded by saying that the ability to classify trends of summary statistics for a broad class of models enhances our understanding of how critical slowing down manifests in complex systems approaching a transition.

Behavior and Ebola: coupling spatial scales and transmission pathways
Andrew Park (University of Georgia)
The recent Ebola crisis in West Africa was challenging to manage in several ways. Two of these challenges pertain to the transmission scenarios that compromised positive behavior change. First, while local transmission events were often curtailed by intervention and transmission-reducing behaviors, they had often already seeded new outbreaks in other locations due to individual movement. Second, the specter of sexual transmission, in addition to contact transmission, emerged during containment phases, raising the possibility of re-ignition of transmission from a neglected pathway.

In this talk, Dr. Park presented two modeling approaches for understanding the dynamical consequences of these phenomena. First, Dr. Park and his collaborators developed an analytically-tractable model that makes use of the assumption that behavior changes limit local transmission before susceptible depletion to develop a time-varying birth-death process capturing the dynamic decrease of the transmission rate associated with behavior changes. Second, they derived an expression for the mean outbreak size of this model and show that the distribution of outbreak sizes is approximately geometric. This allows a probabilistic extension whereby infected individuals may initiate new outbreaks. From this model they characterized the overall epidemic size as a function of the behavior change rate and the probability that an infected individual starts a new outbreak. They found good agreement between the analytical results and stochastic simulations leading to novel findings, including critical learning rates that demarcate large and small epidemic sizes. Next, they developed a simple mathematical model that incorporates contact transmission and sexual transmission parametrized from data from the same 2013-2015 West African Ebola epidemic. The model explores scenarios where contact transmission is reduced following infection events, capturing behavior change, and quantifies how these actions reducing transmission may be compromised by sexual transmission in terms of increasing likelihood, size and duration of outbreaks. They found that sexual transmission can have large effects on epidemic dynamics.

Social deprivation and burden of influenza: Testing hypotheses and gaining insights from a simulation model for the spread of influenza
Ayaz Hyder (The Ohio State University)
Factors associated with the burden of influenza among vulnerable populations have mainly been identified using statistical methodologies. Complex simulation models provide mechanistic explanations, in terms of spatial heterogeneity and contact rates, while controlling other factors and may be used to better understand statistical patterns and, ultimately, design optimal population-level interventions.

In this presentation, Dr. Hyder talked about his extension of a sophisticated simulation model to identify mechanisms for the empirical relationship between social deprivation and the burden of influenza. The modeled scenarios and associated epidemic metrics systematically assessed whether neighborhood composition and/or spatial arrangement could qualitatively replicate this empirical relationship. He further used the model to determine the consequences of local-scale heterogeneities on larger scale disease spread. Dr. Hyder's findings indicated that both neighborhood composition and spatial arrangement were critical to qualitatively match the empirical relationship of interest. Also, when social deprivation was fully included in the model, he observed lower age-based attack rates and greater delay in epidemic peak week in the most socially deprived neighborhoods. Insights from simulation models complement current understandings from statistical-based association studies. Additional insights from his study are: (1) heterogeneous spatial arrangement of neighborhoods is a necessary condition for simulating observed disparities in the burden of influenza and (2) unmeasured factors may lead to a better quantitative match between simulated and observed rate ratio in the burden of influenza between the most and least socially deprived populations.

Ebola virus disease dynamics on distinct risk environments
Baltazar Espinoza Cortes (Arizona State University)
Ebola, first discovered in 1976, can be transmitted from animals to humans and, notably, can be entirely hidden for years between outbreaks. Focusing on a recent Ebola outbreak in West Africa, Mr. Cortes described how this epidemic started with a single case in 2013 in Guinea and caused about 28,000 cases and over 10,000 deaths. While previous outbreaks were self-contained within communities, this outbreak spread from central Africa, impacting big cities and three of the poorest nations. To control disease spread, a cordon sanitaire was introduced to limit travel between different regions. He first presented a single patch model that describes Ebola progression through an SEIDR model; in this setting, S refers to susceptible individuals, E to infected individuals in which the disease is still undetectable, I to infected individuals, D to dead, and R to recovered/removed. Using a Lagrangian approach, Mr. Cortes then introduced a two-patch model that tracks the number of residents and visitors within each patch. This model allowed him to study how mobility impacts disease spread in West Africa.

Can the anti-vaccine movement be modeled as a social contagion leveraging vaccination rate data?
Victor Moreno (Arizona State University)
While vaccines are a great achievement in the field of public health, the anti-vaccine movement has been growing. This is related to a 1998 publication by Wakefield and his collaborators that tied autism to the MMR vaccine. The prevalence of anti-vaccine internet sites has also increased in recent years; on top of this, 52% of internet users are reported to believe almost all or most of the information present on health sites. Motivated by measles outbreaks in California, Mr. Moreno has been studying how the anti-vaccine movement can be modelled as a social contagion using vaccine and population data from CA. His compartmentalized model tracks the number of vaccinated and unvaccinated children and adults in the population. After fitting model parameters to data, Mr. Moreno found that there is almost no recovery from the anti-vaccine epidemic; thus, his work suggests that, in order to improve vaccination rates, we need to focus on educating people who are not already anti-vaccine.

Behavior contagion type and its effect on disease dynamics

Matthew Osborne (The Ohio State University)
Behavior and disease are coupled contagions; for example, disease prevalence influences behavior by increasing the demand for vaccines. Additionally, behavior influences disease progression; for example, HIV-positive individuals may have unprotected sex with other HIV-positive individuals, and this increases the spread of other sexually transmitted diseases. Motivated to develop models that treat this coupling of disease and behavior, Mr. Osborne began his talk by describing the difference between simple and complex contagions. While simple contagions only require one contact to spread, complex contagions require multiple contacts (e.g. peer pressure). Many previous models treat behavior as a simple contagion, but the means of behavior spread is much more complex. Mr. Osborne and his collaborators developed several compartmental models to study the effect of behavior contagion type on disease-behavior dynamics. Considering both simple and complex contagion descriptions, he found that different behavior contagion types lead to vastly different disease dynamics, suggesting behavior contagion type needs to be carefully considered when developing models.

Mr. Osborne completed his talk by describing future plans for his next project; together with his collaborators, he will be exploring whether a Twitter campaign can be used to fight the flu. This project will track how flu vaccination tweets at The Ohio State University impact vaccination behavior on campus. This will allow Mr. Osborne to concretely study the interplay of disease and behavior dynamics.

FRIDAY, MARCH 8, 2018

Behavioral aspects of measles and Zika virus transmission
Benjamin Althouse (New Mexico State University)
Motivated by recent outbreaks of measles in the US and Zika in South America, Dr. Althouse discussed two projects exploring school-level heard immunity against measles and the risk of sexual transmission of Zika. The measles outbreak in the US was linked to low vaccination rates; while vaccine rates are high on the population level, there are pockets of anti-vaccine individuals. Herd immunity plays an important role in containing disease spread: when most of the population is immunized, the presence of a few infected individuals does not lead to an epidemic because the immunized individuals prevent the spread of infection to the remaining non-vaccinated community members. However, when only some of the population is vaccinated, the contagion spreads much more readily through the community. In order to have herd immunity against measles, studies show about 95% of the population needs to be vaccinated. To explore herd immunity, Dr. Althouse built a network model in which schools, each modeled as individual networks, are connected to geographically neighboring schools. His work suggests herd immunity at the school level protects under-vaccinated schools, as well-vaccinated schools help prevent the spread of disease. In the second part of his talk, Dr. Althouse shifted gears to discuss the Zika virus. He noted that there is a strong asymmetry in sexual transmission of Zika as men are infectious for a much longer period than women; moreover, symptoms (and thus knowledge of infection) are also heterogeneous.

Measles, behavioral change models in epidemiology and drivers of vaccine uptake
Frederik Verelst (University of Antwerp)
Despite high vaccination rates, there was a spike in measles cases in Flanders, Belgium last year (369 cases); in Europe as a whole, there were 21,315 cases in 2017. The cases in Flanders were imported by a single family; this case importation, coupled with stochasticity, led to a measles

outbreak. While Flanders has no history of anti-vaccine beliefs, continual vaccine hesitancy and disproportional perceptions of vaccine-related side-effects have impacted vaccine uptake globally. Because vaccination is critical to prevent epidemics, Dr. Verelst is working to identify and quantify what factors influence individuals as they make decisions about vaccination (specifically in Flanders). In his talk, he presented the results of a survey of 1500 individuals in Flanders to study vaccine efficacy, burden of disease, extent of perceived vaccine-related side effects, availability of and reimbursement for the vaccine, local vaccination coverage, and global vaccination coverage. He found that, while all six of these attributes influence the decisions individuals in Flanders make about vaccinations, the extent of perceived vaccine-related side effects and the availability of the vaccine are the most important contributors. This suggests that, in order to produce better models of infectious disease transmission, behavioral change models need to incorporate the impact of perceived side effects of vaccination.

Spring Workshop 3: Disease Ecology and Eco-epidemiology
March 26-30, 2018

Organizers: Hans Heeterbeek (Utrecht University), Mark Lewis (University of Alberta), Joe Tien (The Ohio State University), Pauline van den Driessche (University of Victoria)

Report by: Daniel Linder, Inom Mirzaev, Omar Saucedo

MONDAY, MARCH 26, 2018

The Resurgence of Pertussis: the End of the Honeymoon, Vaccine Failure and Immunity
Pejman Rohani (University of Michigan)
Pertussis, caused by Bordetella pertussis, has unexpectedly reemerged in several countries that had kept high vaccination rates. Pertussis is a serious respiratory disease as it causes approximately 195,000 infant mortalities annually in the developed countries. The reason for the resurgence of Pertussis is unknown. Many have speculated that it may come from the shortcomings of the latest generation of vaccines. In this talk, Dr. Rohani formulated a transmission model comprising of competing hypotheses regarding vaccine failure and challenged them to explain highly-resolved incidence data from Massachusetts, USA. The results paint the clearest picture to date of pertussis' resurgence as the end of the honeymoon period: the predictable consequence of incomplete historical coverage with an imperfect vaccine. They found evidence that the vaccine itself is effective at reducing overall transmission, yet that routine vaccination alone will be insufficient for elimination of the disease. Their results indicate that the core transmission group is schoolchildren. Therefore, efforts aimed at curtailing transmission in the population at large, and especially in vulnerable infants, are more likely to succeed if focused at schoolchildren, rather than adults.

Bistability and asymmetric dispersal in two-patch model with Allee effect
Leah Shaw (College of William and Mary)
Dr. Shaw talked about the Chesapeake Bay native oyster, an important organism for filtering water and a healthy ecosystem and habitat development for other species. Population levels of the Chesapeake Bay oyster have declined significantly since 1880s. Dr. Shaw emphasized that successful oyster restoration depends on initial reef height, and developed a model using 4 differential equations with dynamics capturing: juvenile larval deposition with growth and aging,

an adult aging component with logistic growth, natural mortality, and sediment mortality, reef accumulation and degradation, and sediment deposition with erosion.
Dr. Shaw discussed how under the Allee effect, initial populations below a threshold decline, while those above the threshold can persist. The model displayed bistability, where initially low reefs will degrade but higher ones will persist. She discussed asymmetric dispersal between two coupled populations under the Allee effect, and the bifurcation structure revealed that at high Allee thresholds, there were large parameter ranges in which the globally extinct state is the only fixed point, even though uncoupled populations can persist.

Identifiability and uncertainty in modeling disease dynamics
Marisa Eisenberg (University of Michigan)
Identifiability can be defined as addressing the questions: (1) is it possible to uniquely determine the parameters from the data; (2) is the map from the parameter to the model output injective; (3) are some parameters identifiable even if the whole model is not?
In this talk, the identifiability issues involved in estimating the model parameters are examined using a differential algebra approach. The basic idea is to convert a system of ODEs and measurement equations to a set of monic differential polynomials, only in terms of measured variables and parameters. These represent an implicit form of the map from parameters to output in which the coefficients can be used to test model identifiability. Using examples taken from the recent 2013-14 silent polio outbreak in Israel as well as other disease outbreak examples in several settings, Dr. Eisenberg illustrated some of the potential difficulties in estimating the relative contributions of different transmission pathways, and showed how alternative data collection may help improve identifiability.

Modelling West Nile virus transmission and human infection risk in Italy
Andrea Pugliese (Universita di Trento)
Dr. Pugliese described how an intensified and continuous West Nile Virus has spread across Northern Italy and has been observed since 2008, which caused more than a hundred reported human infections up until 2016, concentrated in two regions, Emilia-Romagna and Veneto. The first positive cases were observed in horses in Toscana in 1998 and WNV-2 has been detected in 2008 in horses in Emilia-Romagna. Indeed, 244 cases of human disease have been observed between 2008-15, with an estimated prevalence of 6% of mosquitoes positive in 2013 and 40% of corvids. Dr. Pugliese calibrated a Bayesian model via MCMC under flat priors that simulates WNV infection in an avian population with seasonal demography on entomological data collected in Veneto in those years. Relevant aspects of the model that were fit were parameter estimates for SEIR host-pathogen mode depending on temperature, mosquito biting rate, host abundance at season start, and prevalence at season start. Two primary assumptions of interest were tested: that the virus is introduced every year at the beginning of the vector breeding season by either infected birds, migrating to the study area, or by diapausing mosquitoes, which were infected the previous year. The results suggest that the infection starts every year in infected mosquitoes, supporting the idea that the virus overwinters in the area. Further, Dr. Pugliese computed seasonal risk curves, indicating the highest probability of human infection is estimated for August, consistent with observations. Finally, multi-year simulations show a qualitative agreement with the observed empirical patterns.

Spatio-temporal patterning of distinct genetic subgroups of Respiratory Syncytial Virus (RSV) in Filipino children

Elisabeth Root (The Ohio State University)
As a virus moves from one individual to another, they also transmit across space which means that they are subjected to different ecological factors in this transmission state. Very little is known about how spatial distance influences viral evolution. The goal of this work is to identify geographic zones in which an event is significantly elevated relative to the rest of a region. This study uses data from a randomized controlled efficacy trial of an 11-valent pneumococcal vaccine (PCV) undertaken in the Bohol province of the Philippines from July 2000 to December 2004. Viral culture and multiplex PCR were done on nasal wash specimens, collected from a sample of infants visiting the regional hospital or outpatient clinics during the vaccine trial. Using Scan Statistic, a list of candidate zones Z is specified a priori. Their main results showed that RSV subgroups arise in distinct localized areas at different points in time, suggesting that effective vaccination strategies require knowledge of which subgroups are prominent in a geographic region and how quickly new subgroups are evolving.

Implications for infectious disease models of heterogeneous mixing on control thresholds
Zhilan Feng (Purdue University)
Vaccination programs aim to attain population immunity above which introduction of more infections won't cause outbreaks. Often public health practitioners estimate population-immunity threshold based on a uniform randomly-mixing homogeneous assumption. This approximation may not be good enough to work effectively because it may require more vaccines than needed. Mixing among sub-populations, as well as heterogeneity in characteristics affecting their reproduction numbers, must be considered when evaluating public health interventions to prevent or control infectious disease outbreaks. For this talk, Dr. Feng developed a new compartmental model to incorporate heterogeneous contact rates in disease transmission and explore the influence of different levels of heterogeneity on the transmission dynamics of infectious diseases using numerical simulations. Their results showed that the higher is the level of heterogeneity in contact rates, the greater is the difference in the disease dynamics observed from those predicted using the homogeneous-mixing models. This means that when the conditions are identical, the speed of transmission becomes slower and the peak attitude becomes smaller. These conclusions have important implications for constructing interventions when outbreaks occur.

TUESDAY, MARCH 27, 2018

Signatures of within-host dynamics of vector-borne diseases at a population level
Lauren Childs (Virginia Tech)
Each year nearly 200 million people are infected with malaria causing parasites that result in half a million deaths. Plasmodium falciparum is the most virulent species which exhibits significant diversity in the parasite population. Mathematical modeling has been a critical component of malaria research. Within-host dynamics of infections, however, vary widely among individuals. In the case of dengue, within-host dynamics differ between primary and secondary infections, where secondary infections with a different virus serotype typically last longer, produce higher viral loads, and induce more severe disease. In this talk, Dr. Childs discusses two examples of the impact of within-host dynamics on population measures of vector-borne infectious disease. In the first example, she discusses a two-part model framework that estimates the diversity as a consequence of different bottlenecks and expansion events occurring during the vector-stage of the parasite life cycle. Her results showed that bottlenecks entering the oocyst stage decrease parasite diversity from what is present in the initial gametocyte population in a mosquito's blood meal. In the second

example, she investigated the role of disease severity (F versus H) of primary and secondary infections with two co-circulating dengue serotypes on the incidence and persistence of the strains in the population. Her findings indicate that these processes can determine whether both strains co-exist, both become extinct, or only one persists.

Mapping zoonotic spillover and urban transmission to estimate yellow fever vaccination impact
T. Alex Perkins (University of Notre Dame)
Although there is an effective vaccine for yellow fever (YF), there is growing concern about the potential for large urban outbreaks due to increased urban growth in close proximity to zoonotic transmission and continued expansion of the Aedes aegypti mosquito that vectors YF virus (YFV). Efforts to inform YF vaccination through transmission mapping have not distinguished between transmission with zoonotic versus urban origins. Dr. Perkins and his collaborators developed a probabilistic framework for disentangling the contributions of these distinct transmission cycles to YF incidence, fitting a combined model of zoonotic spillover and urban transmission to 1,134 YF cases from South America in 2000-2014. Calibrating their model under the assumption that 26.4% (95% CI: 23-30.1) of these cases were urban based on their occupations, they estimated rates of zoonotic spillover that, compared to a baseline with no allowance for urban transmission, were lower in areas estimated to have high potential for urban transmission. Disentangling zoonotic and urban components of transmission enabled Dr. Perkins to calculate location-specific probabilities of a large urban outbreak, which vaccination reduced by 72.33% (95% CI: 20.86-99.97) on average under three different scenarios about vaccination coverage.

Spatial SIS models in heterogeneous environments
Yuan Lou (The Ohio State University)
The spatial spread of diseases in heterogeneous habitats has received considerable attention recently, as the environmental heterogeneity can be an important factor in disease dynamics. The effects of diffusion and advection for a susceptible-infected-susceptible epidemic reaction–diffusion model in heterogeneous environments were examined. Their main goal was to answer the following question: How do movement rates affect the complexity of epidemic models in spatially heterogeneous environment? The existence and uniqueness of the disease free and endemic equilibrium were studied. Dr. Lou concluded that without advection, R0 could be a monotone decreasing function of movement rate of infected populations. With advection, R0 is generally not monotone with respect to movement of infected individuals. With or without advection, the density of infected populations at equilibrium could tend to zero as movement rate of the susceptible populations approaches to zero. However, it is possible to eliminate the infected populations more efficiently with advection.

The Persistence of Foot-and-Mouth Disease Virus in African Buffalo
Jan Medlock (Oregon State University)
Dr. Medlock's talk was about the foot-and-mouth disease virus (FMDV), which is an important trade-restricting livestock disease, for instance a massive FMDV outbreak occurred in the UK, which lead to massive culling of livestock. The African buffalo is an economically important species for tourism and more, and in sub-Saharan Africa, buffalo act as reservoir for FMDV, challenging global eradication and local economies. However, little is known about the dynamics of FMDV in African buffalo. Dr. Medlock's group conducted FMDV infection experiments to quantify epidemiologic parameters of FMDV transmission in buffalo, and a 3-year cohort study to document birth timing, and duration of maternal protection from FMDV infection. Four buffalo were infected with each serotype and measured at 2,4,6,8,11,14,30 days for transmission,

progression and recovery parameters. Based on the experiment different latent periods and transmission rates were estimated for the three different serotypes. Bayesian inference was used to estimate parameters in a five-compartment model that characterized disease dynamics in FMDV in the African buffalo. Strong seasonal birth rates and maternal immunity parameters were assigned gamma prior distributions and the authors constructed a rigorous quantitative framework that explicitly incorporated individual variation in birth rates, waning of maternal antibodies, and epidemiological parameters into predictions about disease persistence from an individual-based stochastic model. Dr. Medlock's group used the model to test the hypothesis that the buffalo's prolonged annual birth pulse may allow for endemic disease persistence, with the latest born calves of one year sparking the new epidemic in the earliest born of the following year's calf cohort. Given parameter estimates, stochastic simulations were run on population herd size of 1000. The conclusions from the simulation were that FMD cannot persist simply via acute transmission, even with varying parameters.

Inferring the interaction between influenza and bacterial pneumonia
Pej Rohani (University of Georgia)
Dr. Rohani's talk emphasized the importance of how current studies of epidemics are typically done in isolation, and how this may not be ideal, particularly since poly-microbial infectious systems may exhibit competitive vs. cooperative and immunological vs. ecological behavior. The public health implication is that significant proportion of mortality events may be attributable to secondary bacterial infection after the primary infection. Histology from deaths from the 1918 flu show bacterial pneumonia in all 58 samples. This has also been observed in more recent pandemics. Experimental results in influenza and pneumococcal bacteria demonstrate that chances of mortality in influenza alone infection are much smaller than influenza cases challenged with pneumococcal bacteria, which was 100% mortality. To infer these interactions, a 3 compartment model with 2 sub-compartments in the susceptible and infectious populations was proposed. These sub-compartments distinguished between those who have been recently infected with influenza. Hypotheses: Infected susceptible may be more infectious than those who have not been recently infected. Susceptibles who have been recently infected are more susceptible. Particle filtering was used to estimate the parameters of the stochastic model. Hypothesis testing from the model fitting to the data were not conclusive about increased transmission impact on strep-pneumococcal from recently infected influenza cases. The susceptibility impact however, indicates that the susceptibility impact was different (increase of 100 fold in mouse models) in individuals with recent influenza. Further simulation and data analysis on different real populations also indicated this to be the case, with the corresponding model fits predicted observed data from various US cities, as well as data from US army camps from 1919.

WEDNESDAY, MARCH 28, 2018

An Examination of Superspreading in Stochastic Multigroup Infectious Disease
Linda Allen (Texas Tech University)
The importance of host transmissibility in disease emergence has been demonstrated in historical and recent pandemics that involve infectious individuals, known as superspreaders, that are capable of transmitting the infection to a large number of susceptible individuals. Recent emerging diseases such as SARS, MERS and Ebola are some examples of outbreaks with superspreading events. To investigate the impact of superspreaders on epidemic dynamics, Dr. Allen formulated a deterministic

and stochastic model that incorporates differences in superspreaders versus nonsuperspreaders. In particular, continuous-time Markov chain models are used to investigate epidemic features associated with the presence of superspreaders in a population. She parameterized the models for two case studies, Middle East respiratory syndrome (MERS) and Ebola. Through mathematical analysis and numerical simulations, she found that the probability of outbreaks increases and time to outbreaks decreases as the prevalence of superspreaders increases in the population. In particular, as disease outbreaks occur more rapidly and more frequently when initiated by superspreaders, the results emphasize the need for expeditious public health interventions.

Epidemic dynamics of cholera in non-homogeneous environments
Xueying Wang (Washington State University)
The transmission of cholera, a water- and food-borne intestinal infection, involves complex interactions among human hosts, pathogens, and the environment. In this talk, Dr. Wang addressed the epidemic dynamics of cholera in non-homogenous environments, with a focus on the spatial variation, seasonal fluctuation and bacterial hyperinfectivity, using partial differential equation models.
Dr. Wang's presentation consisted of two parts. In the first part, she discussed seasonality and spatial heterogeneity. The model she employed is built on a reaction-convection-diffusion system to represent the spatial movement of the hosts and pathogens, and incorporates time-periodic parameters to describe the seasonality of the disease transmission and bacterial growth. Using the next generation method, she defined and analyzed the basic reproduction number of this model, based on which she establishes the threshold type results for cholera transmission in a spatiotemporally heterogeneous environment. In the second part, Dr. Wang developed a new modeling framework to study the effect of bacterial hyperinfectivity on cholera epidemics in a spatially non-homogeneous environment. For the second model, the global threshold dynamics is established. The global attractivity of the unique endemic steady state is derived in a special case. She then investigated the dependence of the basic reproduction number on model parameters by theoretical and numerical means.
Dr. Wang's findings highlight the importance of seasonality, hyperinfectivity and their interplay with spatial variation. The results indicated that the prevention and intervention strategies need to take into account the non-homogeneity of the environments in order to effectively control cholera while optimize the use of available resources.

Community epidemiology: tackling host and pathogen diversities to quantify relevance of conservation biology for public health strategies
Benjamin Roche (Institute of Research for Development, Marseille IRD)
Dr. Roche's talk was about how biodiversity can dilute the transmission of a pathogen, which has been demonstrated in various virus transmission dynamics, such as West Nile and others. Dr. Roche emphasized that zoonotic pathogens exist within a complex environment that involves many hosts and other pathogen species, and that the diversity of host species with low competence for transmitting a given pathogen can reduce the intensity of pathogen transmission, leading to a prophylactic "dilution effect".
Through simulation studies from theoretical models the researchers found that both amplification and dilution effects were equally likely among a vast set of parameters chosen from hypercube sampling. With generalist vectors, those that can bite all reservoir species, the dilution effects are greater than amplification effects. A more detailed work in progress involves analysis when the pathogen is virulent in the reservoir species. Preliminary results indicate virulence on the most

abundant reservoir species is crucial and results from simulation studies indicate that genetic diversity require renewal of the susceptible population with short life spans.

Phylodynamics done "properly": from sequences to dynamics via Sequential Monte-Carlo
Aaron King (University of Michigan)
Dr. King's talk was about using phylodynamics for improvements in the joint information about infectious disease dynamics from pathogen sequences. He explained that most currently available methods first estimate phylogenetic trees from sequence data, then estimate a transmission model conditional on these phylogenies, the consequences of such leading to possible logical inconsistency between the model of transmission and that underlying the phylogenetic reconstruction. Such conflicts in assumptions can lead to bias in the resulting inferences. Dr. King described a general, statistically efficient, plug-and-play method to jointly estimate transmission and phylogeny, which explicitly connects the model of transmission and the model of phylogeny so as to avoid the aforementioned inconsistency. The model uses genetic sequence data to infer transmission properties by exploiting patterns of branching points in the phylogeny, which have information about the dynamics of the disease process. This was modeled by writing the hazards of a branching point in the phylogeny by the usual hazards of disease transmission and the number of ways to observe a branching point given the phylogeny. An example was used from data among young HIV infected black men having sex with men in Detroit. A state space model was proposed to model the HIV infection dynamics in this population, and the likelihood was computed via sequential Monte-Carlo. Conclusions are that joint inference is only available on the order of 100 to 1000 infections. His group is still studying how the algorithms scale to larger problems and important takeaway was that simulation based methods can reveal modeling errors hidden by other methods. Future work is to extend these to hospital infections.

Modeling and control of enzootic West Nile virus transmission: Incorporating avian stage-dependent vector exposure
Suzanne Robertson (Virginia Commonwealth University)
West Nile virus (WNV) is a major public health concern in the United States. While seasonal WNV outbreaks have been widely observed to be associated with the end of the avian nesting season, the ecological mechanisms responsible for this synchronicity are poorly understood. Newly hatched birds, or nestlings, have less feather coverage and fewer defense mechanisms than older birds, rendering them more vulnerable to mosquitoes. While total avian population size increases throughout the season, nestling abundance declines at the end of the brooding season.
In this presentation, Dr. Robertson talks about her investigation on how this temporal variation in host stage abundance may structure enzootic WNV transmission with a novel mathematical model incorporating avian (host) stage-structure and within-species heterogeneity in the form of stage-specific mosquito (vector) biting rates. Dr. Robertson and her collaborators determine the extent to which temporal fluctuations in host stage and vector abundance throughout the season, along with the differential exposure of these stages to mosquito bites, affects the timing and magnitude of WNV activity as well as implications for public health interventions. Specifically, they explore the viability of nestling vaccination as a new form of control in addition to the widely used controls of mosquito larvicide and adulticide.

Qualitative estimation of time-varying contact rates in uncertain epidemics
Jorge Velasco-Hernandez (Instituto de Matematicas, Universidad Nacional Autonoma de Mexico)

The goal of Dr. Velasco-Hernandez's talk was to predict the start, magnitude, and decline of epidemics using observed data. The main idea in the framework is to allow the contact rates to vary depending on a variety of climate, vector population dynamics, disease characteristics, human mobility, climate, demography, vaccination/intervention strategies and others. An iterative algorithm was proposed to estimate the varying contact rates and is theoretically based on the observation of exponential rates of convergence that the interpolation function achieves. The results from comparing to historical outbreaks of measles Zika and Dengue, appear to predict time of outbreaks but not the magnitude of the total outbreak accurately. Asymptotic identifiability was proven as well for the time varying contact rate function.

Resource-driven encounters among consumers and implications for the spread of infectious disease

Rebecca Borchering (University of Florida)

Animals share a variety of common resources, which can be a major driver of conspecific encounter rates. In this work, Dr. Borchering implements a spatially explicit mathematical model for resource visitation behavior in order to examine how changes in resource availability can influence the rate of encounters among consumers. Using simulations and asymptotic analysis, she demonstrates that, under a reasonable set of assumptions, the relationship between resource availability and consumer conspecific encounters is not monotonic. Dr. Borchering characterizes how the maximum encounter rate and associated critical resource density depend on system parameters like consumer density and the maximum distance from which consumers can detect and respond to resources. The assumptions underlying her theoretical model and analysis are motivated by observations of large aggregations of black-backed jackals at carcasses generated by seasonal outbreaks of anthrax among herbivores in Etosha National Park, Namibia. As non-obligate scavengers, black-backed jackals use carcasses as a supplemental food resource when they are available. While jackals do not appear to acquire disease from ingesting anthrax carcasses, changes in their movement patterns in response to changes in carcass abundance do alter jackals' conspecific encounter rate in ways that may affect the transmission dynamics of other diseases, such as rabies. Dr. Borchering's theoretical results provide a method to quantify and analyze the hypothesis that the outbreak of a fatal disease among herbivores can potentially facilitate outbreaks of an entirely different disease among jackals. By analyzing carcass visitation data, she finds support for her model's prediction that the number of conspecific encounters at resource sites decreases with additional increases in resource availability. Whether or not this site-dependent effect translates to an overall decrease in encounters depends, unexpectedly, on the relationship between the maximum distance of detection and the resource density.

THURSDAY, MARCH 29, 2018

Combining Experiments and Models to Understand Disease Epidemics in Insects

Greg Dwyer (University of Chicago)

The economic damage caused by episodic outbreaks of forest-defoliating insects has spurred much research yet why such outbreaks occur remains unclear. An understanding of what determines the timing and severity of pathogen epizootics in forest infects could help mitigate the effects of an outbreak. By using Bayesian statistical approaches to combine experimental and observational data, Dr. Dwyer was able to show that small-scale transmission mechanisms often play a key role in driving large-scale epizootics. Similarly, they have shown that host heterogeneity in infection risk interacts with host density to determine the severity of epizootics of a baculovirus pathogen of the

Douglas-fir tussock moth. Dr. Dwyer used their model to guide the USDA Forest Service to use the baculovirus as an environmentally benign insecticide during tussock moth outbreaks. Combining experimental data with general models of disease spread can thus provide significant assistance to insect pest-control efforts.

Optimal control techniques for managing models with disease dynamics
Suzanne Lenhart (University of Tennessee)
In this presentation, Dr. Lenhart talks about two examples with optimal control techniques to perform management actions in models with infectious dynamics. One model with a system of ODEs has predator-prey interactions with disease dynamics in the predator population; one control action increases the level of infection, causing a decrease in the predator population. The second model is a PDE system representing Zika spreading across a state in Brazil; the control varying in space and time is a vaccination rate.

Modeling zoonoses: the example of Trypanosoma cruzi
Christopher Kribs (University of Texas at Arlington)
Dr. Kribs' talk provided several examples of research questions (and answers) as well as modeling issues involved in modeling zoonoses, using sylvatic transmission of the parasite Trypanosoma cruzi (which causes Chagas disease) to illustrate how host and vector biology, population biology, contact processes, and evolutionary biology interact with transmission dynamics. He considered several kinds of stochastic systems as well as classical systems of nonlinear differential equations. The model he developed allowed for the description of two different R0's that described the competition between two different strains of the disease. Analysis however lead to competitive exclusion, which was not consistent with observed co-persistence of two different strains of T. cruzi. Dr. Kribs then considered several kinds of potential "fixes" so that the analytic model behavior was consistent with observed phenomena: for instance, switching/sharing and host sharing models to describe the observed co-persistence of two different strains of T. cruzi, multiple vector models and stochastic models that incorporating spatial heterogeneity. None were sufficient to explain the observed co-persistence; however, by incorporating seasonality in the transmission process, the deterministic model was sufficient to allow co-persistence for a wide range of parameter values.

Biased population movement and infectious disease dynamics
Zhisheng Shuai (University of Central Florida)
Many recent outbreaks and spatial spread of infectious diseases have been influenced by human movement over air, sea and land transport networks, and/or anthropogenic-induced pathogen/vector movement. These spatial movements in heterogeneous environments and networks are often asymmetric (biased). In this talk, Dr. Shuai presented his investigation on the effects of asymmetric movement versus symmetric movement using several epidemiological models from the literature. These investigations provide a better understanding of disease transmission and control in the real-life application.

Ecology of infectious disease and salmon population dynamics
Martin Krkosek (University of Toronto)
The global expansion of aquaculture has changed the dynamics of infectious diseases in coastal seas. Hydrodynamics allow pathogens to disperse broadly, interconnecting farms into metapopulations of domesticated host fish in regions that also support related species of wild fish.

Spillover and spillback dynamics of pathogen transmission between wild and farmed fish can create novel transmission pathways or bioamplify pathogen abundance, potentially depressing or endangering wild fish. Transport and trade of seafood, feed, eggs, and broodstock bring pathogens into new regions and into contact with native hosts. Density-dependent transmission creates threshold effects where disease can abruptly switch from endemic to epizootic dynamics. Mortality from natural predator–prey interactions may be synergistic or compensatory with these increased infections. Domestic environments may favor the evolution of undesirable pathogen traits, such as virulence and drug resistance, leading to the emergence of strains that cause high mortality and (or) evade treatment. Seafood bioeconomic dynamics can lead to hysteresis and alternate stable states of fishery or aquaculture dominance, which may create a disease trap in coastal seas. Overall, these changes to the dynamics of infectious disease in coastal seas impose new constraints on the sustainability of both wild and farmed fish.

FRIDAY, MARCH 30, 2018

Intermittent Preventive Treatment and the Spread of Drug Resistant Malaria
Olivia Prosper (University of Kentucky)
Intermittent Preventive Treatment is a malaria control strategy in which asymptomatic individuals are given a full curative dose of an antimalarial medication at specified intervals. Constructing studies to understand how IPT impacts the spread of drug resistance is important. The purpose of this talk is to examine a structured model to investigate the relationship between IPTi and IPTc on the spread of drug resistance to malaria, with the following goals: (1) determine the critical level of IPT treatment that would minimize the spread of drug resistance and reduce disease prevalence and burden; (2) determine the optimal timing for IPT drug administration; (3) determine IPT dose that will lead to invasion of a resistant parasite strain, and (4) understand the relative roles of symptomatic treatment and IPT in the establishment of drug resistant strains of malaria. Dr. Prosper found that although IPT treatment can increase the levels and timing of resistant strain invasion, treatment of symptomatic individuals plays a significant role in promoting resistance under the assumptions and parameter values. Moreover, the resistant strain is highly sensitive to the half-life of the drug being administered.

Understanding the ecology of poverty and disease through an integrated ecological-economic framework
Calistus Ngonghala (University of Florida)
Dr. Ngonghala's talk was about developing models to help explain why some human populations remain extremely poor despite current development trends around the world. In the work, he presented a general framework for modeling the ecology of poverty and disease, focusing on infectious diseases and renewable resources. His model incorporated interactions between these ecological drivers of poverty and economics create reinforcing feedbacks resulting in three possible development regimes: globally stable wealthy/healthy development, globally stable unwealthy/unhealthy development, and bistability. The analyses reveal that the proportion of parameters leading to poverty is larger than that resulting in healthy/wealthy development; bistability consistently emerges as a general property of generalized disease-economic systems and that the systems under consideration are most sensitive to human disease parameters. The framework highlights feedbacks, processes and parameters that are important to measure in future studies of development. Importantly, analysis of the model allows for the potential development of targeted and adaptive strategies for effective and sustainable pathways out of poverty.

Heterogeneities in vector-bite exposure and infection distributions: implications for the elimination of lymphatic filariasis
Michael Irvine (University of British Columbia)
Vector biting heterogeneity is believed to be strongly associated with the risk of vector-borne infectious diseases. Understanding the origins of heterogeneity in exposure and risk is important in both control and elimination. Two forms of heterogeneity can characterize the epidemiology of a disease: spatial and individual. These concepts are investigated within the context of lymphatic filariasis (LF), a parasitic, vector-borne disease that has been targeted for elimination.
In this talk, Dr. Irvine presents his findings on heterogeneities in vector-bite exposure and infection distributions. He used infection and mosquito bite data for five villages in Papua New Guinea to understand these relationships before and after the introduction of bed-nets. Dr. Irvine combines village-based analysis with geospatial modelling to quantify both individual and spatial heterogeneity. The introduction of bed-nets increased biting heterogeneity, but the reduction in mean biting more than compensated for this, by reducing prevalence closer to elimination thresholds. He then compares these results to an individual-based model of LF infection to estimate the impact of the number of years to reach elimination. He concluded with his finding that both spatial and individual heterogeneity are qualitatively different and can have profoundly different policy implications.

Modeling Avian Influenza and Control Strategies in Poultry
Hayriye Gulbudak (University of Louisiana at Lafayette)
H5N1 has rapidly spread among wild and domestic bird populations in recent years. With increasing frequency, the virus has shown the ability to infect species which are in close contact with infected birds. Implementing control measures such as culling and vaccination have been helpful to reduce the spread of H5N1. In this talk, a basic SI model of avian influenza is introduced to see how distinct culling strategies impact the disease transmission. The main goal was to construct a model for avian influenza dynamics in domestic birds under the control measure of culling, giving special attention to these different culling strategies. Their results suggest that in addition to culling, timely implementation of temporary control measures such as isolation of poultries from wild birds and movement ban of all poultry and hatching eggs can be crucial for reducing the number of infected domestic birds to a low equilibrium level or for eliminating the disease in poultries.

Spring Workshop 4: Multiscale Dynamics of Infections
April 23-27, 2018

Organizers: Rebecca Garabed (The Ohio State University), Juan B Gutierrez (University of Georgia), and Grzegorz Rempala (The Ohio State University)

Report by: Colin Klaus, Megan Powell, Omar Saucedo

MONDAY APRIL 23, 2018

Dynamic Models of Malaria
Eberhard Voit (Georgia Tech and Emory University)
Disease represents a specific case of malfunctioning within a complex system. Whereas it is often feasible to observe and possibly treat the symptoms of a disease, it is much more challenging to

identify and characterize its molecular root causes. As an illustration, a case study of malaria which affects more than 200 million people worldwide and kills about half a million individuals per year. While malaria is initially a disease of the blood, it quickly affects other tissues and organ functions and triggers uncounted responses of the host's defense systems. In all types of malaria, the sporozoite form of the Plasmodium parasite enters the human or NHP host through a mosquito bite. Moving quickly with the blood stream, the sporozoites soon reach the liver, where they infect hepatocytes. The molecular events, host-pathogen interactions, physiological host responses, and the global reach of the disease create a truly multi-scale system.

Transcriptomics is generally viewed to be the most reliable source of omics information. However, its output is not always easy to interpret in terms of phenotypical outcomes, as gene expression is two or three steps removed from metabolic, immunological, or physiological manifestations. Faced with this challenge, the speaker employed computational modeling to interpret transcriptomic information. The consistency among species and the correlation with the degree of parasitemia suggest that the changes are not merely spurious occurrences. Also, at first glance, the results seem to suggest that more hypoxanthine and inosine are produced because the parasites require them. However, such a casual interpretation of the results requires caution and careful consideration.

Transition Dynamics Convey Key Programs in Cellular Populations
Caleb Bastian (Princeton University)
Cancer is a complex multi-step process. The Epithelial Mesenchymal Transition (EMT) is a key cellular program of growth and development of mature cells, such as in wound healing. Moreover, evidence for its role in pathology, such as cancer invasion, has been accumulating following from intensive study. However, little is known about the dynamics of the transition and its role in conveying distinct gene programs. Here these dynamics are modeled using input-output maps by ODE's, PDE's, and global sensitivity analysis.

The global spatiotemporal distribution of metastatic (dysregulatory) burden is found to be critically sensitive to key non-linear dynamics. With hysteresis, continuous or pulsed input given to the system leads to bistable output whereas without hysteresis the output is monostable. Aim became to find those parameter values in the model that describe the size variability of the output region's area. In this study, a small set of parameters was found to identify approximately half of the variation for the in silico model. At a wet-bench these effects were found at the pM concentration scale, which the speaker noted is the limit of what's experimentally possible to measure. (Spatial effects, too, can be important because the input can become output and then diffuse to neighbors.)

Disruption of the hysteresis bifurcation – by CRISPR editing – was found to greatly diminish the ability of invasive malignant cells to be malignant in mice animal models. This promotes the philosophical view on biological systems that small alterations in key components cause permanent macro-level changes and that the system complexity can be reduced to a small set of “drivers” where other aspects of system are adapted to those drivers.

Hybrid models predict emergent dynamics of multiscale cell populations
Neda Bagheri (Northwestern Department of Chemical and Biological Engineering)
Computational models are essential tools that can be used to simultaneously explain and guide biological intuition. With increasingly high-resolution, high-throughput, and dynamic experimental data computational biologists are better equipped to develop informed models to characterize

complex cellular responses and direct experimental design. The author introduced an agent-based model as an intuitive, modular, and flexible framework to interrogate the inherent multiscale nature of cells – reinforcing how "the whole is greater than the sum of its parts" – and to predict cell population dynamics from the composition of simpler biological modules. Tumor growth was compared when in a vacant environment or when surrounded by a matrix of healthy cells. Simulations show tumor spread is not as great when in healthy tissue and also that the proliferative rim – agents in the proliferative state – is blurred and spread throughout the tumor. The circularity of the tumor boundary – a measure often used for assessing tumor malignancy – is found to depend on the environment tumor is in. Healthy tissue was found in silico to be better suited to maintaining that circular boundary.

In silico, growth of the cancer necrotic core was critically linked to the diminished efficiency of the vascular system to meet the nutrient needs of cancer tissue, a feature that perhaps has not been duly recognized. A future step is to incorporate the immune response's effect in this agent based model, especially because immunotherapy is emerging as an important treatment for cancer. In summary, elucidating the compositionality problem is fundamental to advancing our understanding of basic science: to promoting the impact of synthetic biology and to designing precise dynamic therapeutic strategies.

The population genetics of pathogen virulence
Todd Parsons (Laboratoire de Probabilités, Statistique et Modélisation, Sorbonne Université)
What is virulence? Increased virulence is considered as increased host mortality rate. Why is there so much variation in virulence across antigens? To answer questions about virulence, first an individual based model (IBM) is considered, capturing a basic SIR model, with multiple strains of the pathogen. The model is considered as a continuous time Markov chain where events happen at random times, with exponentially distributed times. Actual population size is considered a random variable and a density dependent transmission is used, dividing the mass action infection term by n, the size of the arena, not the population. Then the law of large numbers is used, with the assumption that the population is large and the initial conditions are random. The deterministic equation describes how to analyze the stochastic model. An assumption of competitive exclusion means the pathogen with the bigger R0 will drive where the stable fixed point occurs. If the model is initiated a perturbation away from equilibrium, virulence affects the fixation probability, unlike starting at equilibrium, where fixation probability only depends on R0. This implies it pays to be less virulent if there is an overpopulation of susceptibles. There is always going to be a push towards reduced virulence in a weak selection regime. Selection will favor the less virulent strain.

Additionally, a stochastic version of adaptive dynamics is considered where the contact rate depends on virulence which means R0 is dependent on virulence. The endemic equilibrium in turn depends on virulence as well. The virulence is used to create a trait substitution sequence making jumps from one virulence to the next, where a mutation either replaces the current state or does not and the system stays the same. In conclusion, not all R0s are the same, finite population size matters. When two strains with close to the same R0 compete, the one with the lower virulence will have a competitive advantage.

TUESDAY APRIL 24, 2018

Challenges when building a continental scale livestock disease spread model: Animal movements, farm locations, and computation

Tom Lindström (IFM, Linköping University)

Foot-and-mouth disease affects all cloven-hoofed animals and is painful for the animal and costly for livestock owners. The US livestock industry is dominated by cattle, but there have been no outbreaks since 1929. If there were to be an outbreak, the US Department of Homeland security needs to know how to best control it. Applied epidemiological modeling offers powerful tools to inform policy decisions regarding control actions, identify spatial hotspots, or predict the course of the outbreak. However, modeling efforts for US cattle movement is challenged by limited information about the system. There are no federal databases with animal movements that can be used to model disease spread via these contacts. In contrast, movement data for the EU is easily available because legislations require member countries to keep databases on all movement of cattle.

The study considers a stochastic SEIR model, at the individual US farm level. Two processes of disease transmission are considered, a kernel approach for local spread and through animal movements. This approach has led to the United States Animal Movement Model (USAMM). The model is informed by data collected from cattle moving across state lines where interstate certificates of veterinary inspection are required. Researchers worked to get 10% of the paper veterinary inspection records, but since this is such a small sample, a model is needed to extrapolate in order to simulate the entire network of US cattle movement. Therefore a probability model was developed for movement between counties with a decreasing probability as distance increases between counties. Currently two parameters are estimates for the spatial kernel as well has "historical flow" of cattle. Using hierarchical Bayesian model, researchers are able to fit parameters to find movement out of particular states and validate with current cattle movement data. While the model fit well for the big picture, some did not, especially underestimating some highly connected states.

Exploring the role of geographic scale on foot and mouth disease outbreaks

Lindsay Beck-Johnson (Colorado State University)

Foot-and-mouth disease outbreaks are influenced by factors at different geographic scales from the local, regional, and national level. The talk focuses on understanding the effect of local and regional factors on national patterns of potential foot and mouth disease outbreaks as well as how incorporating variation form multiple models in forecasts. The US has not seen an outbreak of FMD since the early 1900s, so data from other countries needs to be used to assess risk factors and efficacy of control for potential US outbreaks. The study starts by using a US disease outbreak simulation which is a national level simulation for exploring potential FMD outbreaks in the US. Study has updated the model to bring it down in scale down to the farm level, using the farm location and agricultural production simulator (FLAPS). The study looks at multiple outbreak metrics including the number of infected cattle and farms, epidemic extent and percent of local or shipment transmission. The model predicts the number of infected cattle and farms, predicting a high number of outbreaks in the central plains. Farm locations can drive very different results in order to understand national scale patterns. Local transmission also drives percent of transmission from local spread. Shipments are also important for moving infection to new areas.

How can control change outbreak patterns? Potential control strategies include movement bans, culling, and vaccination with input from USDA subject matter experts.

Scenario 1: Culling of both infect farms and dangerous contacts with a movement ban (Culling strategy)
Scenario 2: Culling infected farms and vaccination of dangerous contacts with a movement ban (vaccination strategy)

The model predicts both strategies reduce outbreak in similar ways. For the distribution of the percent of local spread and percent of shipment spread, vaccination is a better strategy.
In conclusion, the addition of the farm level information has captured geographic patterns at local and regional scales that impact the predictions about potential FMD outbreaks.
In the second part of the talk, ensemble modeling is considered to look at multiple model directions. Data can be aggregated from data sources such as climate change and implemented control. Study used Bayesian reliability average ensemble because it works on relatively small amounts of data, does not require parameter fitting to data and uses summary statistics. BREA weights the models by a biased criterion with weights dependent on how well each model predicts outbreak. The ensemble model does not depend on existing data, but can use outbreak data to be validated. Study considers model transmission using four different models. Preliminary results indicate the BREA methodology will be a good framework for developing policy making decisions for potential outbreaks.

Modeling Endemic Foot and Mouth Disease in Cameroon
Laura Pomeroy (Ohio State University)
Foot-and-mouth disease causes devastating economic lost to farmers. It's a disease of livestock affecting cloven-hoofed domestic and wild animals worldwide. Foot-and-mouth disease is one of the main diseases limiting animal production and trade, contributing towards food insecurity in regions with a high demand for animal protein for an increasing human population. Endemic disease dynamics occur throughout Asia and Africa; however, most models of infectious disease dynamics represent locations throughout North America, Europe, and Australia that experience epidemic dynamics or have been FMD-free for decades. In Cameroon, five serotypes of FMDV are endemic with no formal control. The causal agent of FMD is a highly variable small RNA virus and is a member of the family Picornaviridae. As with other picornaviruses, FMDV is non-enveloped and contains a positive sense RNA genome within an icosahedral capsid composed of four structural viral proteins (SP) named VP1, VP2, VP3 and VP4.

The objective of this talk is to determine the serotype (s) of FMDV naturally circulating in the Far North region of Cameroon using serological evidence of infections in cattle and viruses obtained from clinical or subclinical FMD infections in Cameroon. This study was conducted by performing the following task: survey cattle to find the extent of FMDV seroprevalence, quantify the duration of the antibody response in cattle, quantify transmission in cattle, and determine best practices for control in this endemic setting. They concluded that serotype specificity in FMDV infection with regards to the nature of endemicity, transmissibility, and duration of immunity. Multiple populations maintain FMDV in the Far North Region of Cameroon. Another observation was that the addition of serology data, host age and sampling for multiple serotypes allows the catalytic model to inform about disease dynamics. Finally, vaccination against SAT1, Type O, Type A is a viable control strategy.

Multiscale Challenges in Modeling the Initial Spatial Spread of an Infectious Pathogen

Julien Arino (University of Manitoba)
With travel becoming easier and more affordable, understanding the initial phase of spread of an infectious pathogen is critical for effective intervention. Indeed, determining which locations are the potential "next targets" of a budding epidemic helps public health authorities allocate resources more effectively, which can in turn bring the nascent event under control before it reaches epidemic scale. The 2009 H1N1 influenza pandemic provides a unique opportunity for detailed examination of the spatial dynamics of an emerging pathogen. In the United States, the pandemic demonstrated a heavy geographical heterogeneity in which the spring wave was limited mainly to northeastern cities while the wave in the fall affected the whole country.

To determine the relative contributions of population movements, demographics, school openings, prior immunity, and environmental factors to pandemic spread, they fitted a series of mechanistic models to our highly resolved US influenza surveillance datasets. In order to keep track of the pandemic, weekly epidemic indicators of the number of influenza-like illness patients were sorted by zip code giving information about 271 administrative locations with covered 90% of the US population and 48 states. Their results contrast the previous modelling studies that indicated that environmental factors, population sizes, and long-distance transmission events (air traffic) are major determinants in disease spread. They concluded that the 2009 pandemic autumn wave spread slowly because transmissibility of the influenza virus was relatively low and children (who travel long distance far less than adults) were the predominant sources of infection.

Pairwise Survival Analysis: Contact intervals, regression, and phylogenetics
Eben Kenah (Ohio State University)
When integrating epidemiologic data with pathogen phylogenetics, the likelihood for the transmission model is often a branching-process likelihood based on a generation interval distribution and offspring distribution. However, in general an epidemic does not go like a branching process. When you approximate the early spread of an epidemic with branching process, to be valid not only must mass action hold, but also the R0 must be near 0. In fact, a misspecified likelihood can lead to severely biased estimates with or without a pathogen phylogeny. Writing the likelihood as a survival likelihood with failure times in pairs---a process we call pairwise survival analysis---accounts for time spent at risk of infection. In a simple example with three infections, we show that a pairwise survival likelihood produces more accurate source attribution and parameter estimation. In a mass-action model with negligible depletion of susceptibles, the pairwise survival likelihood depends only on information about infected individuals in the limit of a large population. However, this asymptotic likelihood has cumulative hazard terms that have no counterpart in a branching process likelihood. As an example of the flexibility of pairwise survival analysis, we describe a pairwise accelerated failure time model that can be used to estimate covariate effects on infectiousness and susceptibility. This model---modified to account for the buildup of immunity---was used to estimate the efficacy of the Ebola vaccine based on the WHO ring vaccination trial in Guinea. This trial collected data on individuals exposed to infection who escaped as well as Ebola virus genetic sequences.

Finally, a pruning algorithm for calculating an approximate likelihood using both epidemiologic data and a pathogen phylogeny was shown. Pathogen genetics can improve statistical efficiency and reduce bias – for example if external infections are identified -- but this depends on good epidemiologic study design and a good likelihood for transmission. This finding was in the context of a virtual 300 household study, each of size 6. Those models using phylogeny – and the

nature of how the disease spread -- in practice took a possible 19000+ candidate, transmission trees down to 4 when applied to past outbreak data. As a note, most pathogen evolution occurs within hosts so the phylogenetic and transmission trees can have different topologies.

Local and regional dynamics of arbovirus transmission: the role of mismatched spatial heterogeneity

Sean Moore (University of Notre Dame)

There are several occasions where mathematical models are fitted to epidemiological time series, which must inevitably be aggregated at some spatial scale. Weekly case reports of chikungunya have been made available nationally for numerous countries in the western hemisphere since late 2013, and numerous models have made use of this data set for forecasting and inferential purposes. In this talk, models at three different spatial scales to weekly case reports from Colombia to explore limitations of analyses of nationally aggregated time series data. The vector-borne disease that was explored was Dengue. They fitted versions of this model specified at different spatial scales to weekly case reports aggregated at different spatial scales: single-patch national model fitted to national data; single-patch departmental models fitted to departmental data; and multi-patch departmental models fitted to departmental data, where the multiple patches refer to municipalities within a department.

They found that model consistency with epidemic dynamics improved with increasing spatial granularity of the model. Specifically, the sum of single-patch departmental model fits better captured national-level temporal patterns than did a single-patch national model. The model performed better when posed at finer spatial scales, due to better matching between human populations with locally relevant risk. Confronting spatially aggregated models with spatially aggregated data imposes a serious structural constraint on model behavior by averaging over epidemiologically meaningful spatial variation in drivers of transmission, impairing the ability of models to reproduce empirical patterns.

WEDNESDAY APRIL 25, 2018

Multiscale Modeling the Transmission of Infectious Diseases

James Hyman (Tulane University)

Models provide a framework for the analysis, prediction, and understanding of the spread of an infectious disease. They can help understand and predict how a disease will spread to assess and optimize intervention and prevention strategies. For epidemiology models we always look for the basic reproductive number, but basic SIR models are too simplistic. Infectious period can vary per person and how infectious you are changes as well as changes human behavior. A new model with infectious stages can be used, but mathematicians need to not get too lost in the trees and not see the woods. Both space and time can be considered, but totally different epidemics can still occur. For example, between 1700s and 1800s, two different flu epidemics spread totally differently due to the creation of the railroad between those years. Hong Kong flu spread very differently in two subsequent years in the 1960s since susceptibility changes after exposure.

HIV modeling can be dramatically affected by biased mixing and care needs to be taken when interpreting 95% confidence intervals which are on the model and not on the epidemic. Journal articles are often taken out of context and the press will disseminate false information by focusing only on figures so caveats in model conclusions need to be included in published figure captions.

Uncertainty quantification is becoming increasingly important and policy makers need to be clear that simulations are approximation of reality and when making policy decisions. Today it is not if something can be modeled it is how well it can be modeled and no model is better than a bad model that gives us confidence that we understand reality

A pandemonium of parasites: predictability in the face of complex parasite interaction networks?

Anna Jolles (Oregon State University)

When are multiscale disease models needed? Realism at the cost of generality/tractability but predicting disease patterns requires mechanistic models when biotic and abiotic environments are changing quickly. Moving animals, food, wildlife moves parasites around the globe, we get new mixes of parasites and pathogens. Climates and habitats are changing and human population growth creates changes in diseases. This study focuses on interactions among co-infecting parasites as drivers of disease outcomes and dynamics. Using African buffalo and their parasite community as a model system, the study considers co-infecting parasites contributions to incidence and duration of concurrent infections, perhaps forming a modular interaction network. African buffalo are ecologically and economically important and carrier of many important pathogens. As close relations to livestock so they get many of the same infections as cattle and populations are large and social so they are a good species for modeling disease transmission in a natural population. Radio-collared buffalo were captured every 6 months for monitoring of infections including tick borne pathogens and GI parasites

First researchers looked closely at Mycobacterium tuberculosis and studied how GI helminths affected bTB dynamics. A helminth removal experiment with four-year field experiment with 200 radio collared buffalo in two herds was treated half the buffalo with long lasting anthelmintic drug. Unfortunately treatment did not reduce the risk of acquiring TB at all. But treatment did reduce mortality in TB positive buffalo compared to controls. As a result, R0 goes up with treatment but unclear whether treatment affects infectiousness. Overall, co-infections often have strong effects on disease dynamics and outcome for the but which parasites are key and why remains unclear. TB can cause shifts in parasite community structure and variation in host-pathogen interaction may underlie some of the observe parasite associations. There is a need to investigate mechanisms underlying these findings, to understand how general they are and if TB infection is unique in its coinfection dynamics.

Transmission and infection dynamics of Clostridium Difficile

Cristina Lanzas (Population Health and Pathobiology, NCSU)

Clostridium difficile is an anaerobic human pathogen that forms spores, produces toxins and resides in the gut. Clostridium difficile infection (CDI) is an important hospital acquired infection and the most common cause for diarrhea there, in serious cases a cause for pseudomembranous colitis, and even possibly death. Not only is it a common health care infection but in 30% of cases there is recurrence even after antibiotic treatment. Antimicrobial therapy is often even a strong and independent risk factor for CDI because it disrupts the indigenous microbiota, which provides protection against C. difficile colonization.

In the last decade, the incidence and severity of C. difficile infection has increased at alarming rates throughout North America, especially in the elderly. Despite this, the transmission control protocols in hospitals have remained essentially the same. Epidemiological and within host

models for Clostridium difficile and integration of both scales were discussed. The multi-scale aspects are at the epidemiological scale through individual heterogeneity in susceptibility – captured through agent based modeling – and clinical level data but also within the host scale, such as the immune system and host-associated microbial communities. Here the speaker et al took the probability of colonization as proportional to patient susceptibility – the risk associated to antibiotics give -- and contamination status driven by ward level contamination through individual room cleanliness and isolating severely infected individuals. This was a departure from what had been done elsewhere.

Epidemiology of Environmentally Transmitted Infections: Models and Empirical Data
Renata Invanek (Cornell University)
For environmentally transmitted infectious diseases (ETIDs), which spread through the contaminated environment (such as foods, surfaces and fomites), there is a lack of consensus about the mathematical approach to derive the reproduction number R0, which leads to inconsistent predictions about the spread and control of these infections in their host populations. The purpose of the talk was to explain three current approaches to derive a theoretical expression for R0 for ETIDs and assess their validity through comparison with available empirical data. To test the approaches, Salmonella was considered in laboratory mice in which served as a basis for the theoretical and empirical model. The three conflicting theoretical expressions for R0 were derived using the next generation matrix approach according to three unverified hypotheses about the role of the environmental phase in the transmission of ETIDs.

When testing for the theorical R0, the existing theoretical R0s for ETIDs disagree in their interpretation of the role of the environmental phase in the transmission of these infections. It is unclear which, if any, of these interpretations of the role of the environmental phase is valid. Here they used Salmonella Typhimurium in laboratory mice as a theoretical and empirical model system and assessed the validity of these interpretations by comparing theoretical predictions with estimates of true R0 from published experimental data. All three theoretical R0 expressions were considerably different. However, the results were used to derive future study designs that would allow conclusive identification of the valid hypothesis and its corresponding theoretical R0. The work presented may serve as a template for an integrated empirical and theoretical approach to study R0 in the epidemiology of ETIDs.

Modeling the temporal evolution of the host immune response to infection
Michael Kirby (Colorado State University)
Dr. Kirby presented two explorations into the temporal dynamics of the host immune response. The first concerns the real-time modeling telemetry data generated by collaborative cross (CC) mice. Radial basis functions were used here overcome the curse of dimensionality through an appropriate choice of centers. Parameterizing the RBF's was reduced to a linear programming, convex optimization problem. The method is very fast.

CC mice in a study were monitored in a healthy state for seven days and are subsequently challenged with a salmonella infection. Evidence of infection in the gene expression data is almost immediate (which is why authors in human trials are advocating to collect blood samples very frequently the first couple days of a later DARPA study that attempts to inoculate subjects against several different infection types). Temperature ad activity data is collected at one minute intervals and modeled in real time using a method for time-series prediction that also serves as a novelty

detector to quantify time to symptoms and full-blown infection. The analysis seeks to identify and characterize aspects of tolerance to high pathogen loads exhibited by certain CC lines. For geometric data analysis: understanding the geometric structure of data is critical for algorithm design, mathematics provides insight into data reduction, manifolds are useful model for capturing nonlinear variations, the geometric framework of Grassmanians, Stiefels, and flags provide robust approaches to capture structure in large volumes of data.

Micro and macro SIR models
Grzegorz Rempala (Ohio State University)
Recently, there has been considerable interest in both inference and predictions for compartmental epidemic models on multiple physical scales - for instance, a single host and a population of hosts. Both viral invasions and global pandemics are often described by similar mathematical constructs known as SIR models. SIR Models for predictions can create confusion and not appropriately predict disease spread. We may not be looking at the models as carefully as we should be. The simplest issue is SIR models is an aggregation, where we fit an average. The CDC was criticized for using too simplistic of a model for the recent Ebola outbreak. Epidemiology data from field studies is often problematic since most observational data is often censored and/or lumped. Can we consider outbreak SIR type macro models from a micro perspective?

On a micro level, the Gillespie algorithm can be used as a simple stochastic SIR model using the law of mass action. The trajectory equation can be written assuming a Poisson process, in which the argument of the process which accumulates pairs of potential interactions between S and I. A basic assumption for this is that the population is uniformly mixed. Rates become very important to drive counts on the individual level. But the data does not always follow this process, since data can still be lumped.

Overall there are different ways of looking at SIR models. Models can be created that say something about individual transfer or failure times where transfer times for individuals are independent. This can create a highly efficient sensor network instead of following entire population, the number of individuals is fixed, but they are checked on a regular basis to see when they fail. Information is carried in the timing of the event because it is connected to the amount of hazard and once enough data is collected, the entire set of SIR graphs can be recovered.

THURSDAY APRIL 26, 2018

Multiscale Systems Biology: A Case Study Linking Molecular Dynamics to Epidemiological Processes of Malaria
Juan B. Gutierrez (University of Georgia)
The advent of high-throughput molecular technologies in particular, and the broad availability of data, in general, have forced the quantitative biology community to rethink how to conceive, build, and validate mathematical models. In this talk I will demonstrate how molecular and cellular processes are related to the epidemiology of malaria. We will explore (i) asymptomaticity at the epidemiological level. In Colombia there is a studied problem because the percentage of self-reported, dire cases of malaria is much less than the latent affected population that can tolerate the infection and spread it. For example, if you die from malaria, this would likely happen the first time you become sick with it. After first infection, later episodes are less severe. These asymptomatic cases are very important reservoir for malaria infection. Earlier compartmentalized

models could not explain the structure of the reservoir because they do not account for the geographic vector born movement.

Here the authors modeled the geography using splines to try to account for mosquito and human migration patterns across the real country landscape. (ii) telemetry analysis identifying a systemic response to the disease before traditional symptoms show, (iii) the cellular models that explain this phenomenon as an interaction between the immune system and infected red blood cells – from looking at gene data, the immune system seems to respond as if it were a virus – , (iv) mathematical models that link cellular and transcriptional time series, (v) transcriptomic analysis, and finally (vi) high-throughput in silico drug discovery to solve an epidemiological problem. All these linked analyses provide a comprehensive picture that no single scale can produce alone. The usefulness of models under this light takes on new meanings, and this broad scope requires the cooperation of scientists coming from very different intellectual traditions. In this talk authors also presented how an information system that delivers Adaptive Learning for Interdisciplinary Collaborative Environments (ALICE) is used to train scientists in this new normal. ALICE is a web based information system for adaptive interdisciplinary experiential learning with two modes (i) interest based for interlesson assignments (ii) interest based for capstone projects. ALICE fills a gap in interdisciplinary training.

Identifiability Issues of an Immuno-Epidemiological Model: The Case of Rift Valley Fever Virus
Maia Martcheva (University of Florida)
Differential equations are powerful tools for modeling biological systems with broader applications to the fields of biomedical research and infectious disease modeling. In particular, ODEs have been a useful tool for determining the unknown parameters of theoretical models confronting experimental data. Identifiability analysis is a common methodology to determine unknown parameters in ODE models. Even though identifiability analysis has been used for over the last two decades for ODE models, including structural, practical, and sensitivity-based identifiability analysis, the identifiability analyses of age-structured PDE models have not been studied. The overall objective of this talk is to discuss structural identifiability issues for an immuno-epidemiological nested vector-host model with application to Rift Valley Fever disease.

Rift Valley Fever virus is a pathogen transmitted mainly through mosquitoes and may infect several different mammal species causing illness and death in livestock species and humans resulting in millions of dollars of economic loss. From the structural identifiability analysis, they found the immunological model is not structurally identifiable for the measurements of time series viremia concentrations in the host. Therefore, they proposed the non-dimensionalized and scaled versions of the immunological model and showed that they're both structurally identifiable. From a modeling and biological perspective, it is clear that with-in host dynamics have an effect on the between-host disease transmission.

Vector-Borne Pathogen and Host Evolution in a Structured Immuno-Epidemiological System
Hayrirye Gulbudak (University of Louisiana at Lafayette)
Vector-borne disease spread is the most common dissemination mode, causing many diseases and epidemics in history. The vast majority of vector-borne vertebrate infecting viruses are responsible for a number of severe diseases in human and livestock. Thus, it's important to understand how vector-borne pathogens evolve. However, there are few theoretical studies on virulence-transmission tradeoffs and evolution in vector-borne pathogen-host systems. In this talk, Dr.

Gulbudak considered an immuno-epidemiological model that links the within-host dynamics to between-host circulation of a vector-borne disease. In particular, the provide a nested approach to study vector-borne pathogen and host evolution, allowing us to examine virulence evolution in response to vector inoculum size. The question that they wanted to answer is: what are the optimal evolutionary host and virus strategies and how vectors can influence coevolutionary trajectories of host and parasites?

By considering multiple pathogen strains and multiple competing host populations differing in their within-host replication rate and immune response parameters, respectively, they derive evolutionary optimization principles for both pathogen and host. Invasion analysis shows that the basic reproduction number principle holds for the vector-borne pathogen. In particular, the pathogens evolve towards maximizing its reproduction number. The parasite replication optimality curve is an increasing monotone function of a host trait. When the immune response is smaller, the optimal parasite replication rate decreases resulting in larger parasite fitness. The speaker urged that future work needs to be done to asses both impact of vaccination in immune-epidemiological parasite-host systems and further computation of evolutionary stable strategies.

A Categorization Framework for Multiscale Models of the Dynamics of Infections
Winston Garira (University of Venda-South Africa)
The development of multiscale models of the dynamics of infections is a scientific endeavor whose progress has so far resulted in the development of a wide variety of multiscale models of the dynamics of infections with different structure and mathematical representations which are associated with the different levels of organization of an infectious disease system (cell level, tissue level, host level, etc.). In this talk I will present a framework for categorization of multiscale models of the dynamics of infections. Such a categorizarion framework is useful in categorizing and classifying the different types of multiscale models of infection dynamics and in turn in bring some order to the discussion on the structure of multiscale models of infectious disease systems.

Pathogenic diseases depend critically on intricate interactions between pathogens, hosts, and their environment. Hence infectious diseases are multiscale, multi-level problems with high complexity. Speaker proposes that we need a more sophisticated way to categorize such models. Speak began by noting these may be grouped into empirical models that are data driven and quantitative multiscale models which are mechanistic. The latter class are the only ones which can be predictive. Terms system, level, scale, entity and component are used as a taxonomy for partitioning of infectious disease systems. System used to emphasize the system analysis. A level is considered a layer above a scale. A scale if used to sub-partition the level. Entity is a constituent element of a single scale; a component is any level scale or entity of infectious disease system. An infectious disease system is then characterized through the properties: openness (determining system boundaries), its relation to history (past behavior shapes the future), emergency (patterns at upper scale emerge from the lower level interactions), co-evolution (all organisms involved impose selection on one another), self-organization (robustness emerges from local interactions across levels and scales).

Incorporating Within-host Heterogeneity into Transmission Models
Lauren Childs (Virginia Tech)
Mathematical models are a key tool in the study of the spread of infectious diseases such as influenza, malaria and dengue. In particular, transmission models have been successful at

determining the most promising intervention strategies, despite the fact that many of these models assume all individuals experience identical infections. For example, Malaria, HIV, and TB present many mathematical challenges in infectious diseases, and there exist many critical knowledge gaps to accurately parameterize the models. One of the aspects that make modeling these diseases difficult is the pathogens genetic diversity which alters prevalence and transmission along with heterogeneous behavior that influences exposure. In malaria, sustained parasite proliferation in the blood by the most virulent species Plasmodium falciparum may lead to a chronic phase of highly variable intensity and duration. Infection with HIV is incurable, which removes the need to estimate heterogeneous parameters of recovery and immunity, but complex within-host dynamics lead to variable infectious periods. For tuberculous, most new infections result in an asymptomatic "latent" infection, with innate immunity controlling bacillary growth in the lung.

Heterogeneous within-host dynamics for all three infections make it difficult to establish the timing and duration of latent or chronic infection periods, where transmission potential may differ significantly from acute infection. As a result, modelling the impact of individual-level interventions on population-level transmission is challenging. Therefore, mathematical models can provide a powerful framework to construct possible impactful interventions, identify areas where more empirical work is needed, and focus on policy and research questions that minimize the disease outbreak.

Analysis of the Plague at Eyam
Daniel Linder (Georgia Health Sciences University)
The rodent-flea-human transmission route of Y. pestis is widely known and has been medically confirmed to cause the bubonic form of plague. The plague at Eyam was a serious outbreak in 1665 originating with flea infested cloth. For this outbreak, a very detailed data set is available and villagers were encouraged to self-quarantine implying an essentially closed population, making it ideal of model fitting. Data suggests that over the 14 months it infected the town, the plague initially decreases but then comes back stronger. The observed rapidity of the outbreak during the second pandemic appears to have happened on timescales that are not readily explained by this transmission mechanism alone. The researchers present a statistical method to analyze such data that is capable of distinguishing the important mechanisms of outbreak dynamics. First a mass action model is considered where counts of species with reaction rates are used to infer based on the likelihood. Parametric bootstrapping is used to produce summary statistics by using diffusion approximations or linear noise approximations in a more computation efficient a process such as the Gillespie algorithm. Additionally, an algebraic statistical model is described.

For the plague data, the model found the human-to-human transmission parameter to be 5.3 and recovery parameter to be 4.22 with the rodent-to-human transmission parameter to be 0. Bayesian analysis of historical data for plague suggests human-to-human transmission of plague via ectoparasites (human lice and fleas) best describe the data but at Eyam however the plague pneumonia model fit just as well as ectoparasites. Overall rodent-to-human transmission was much lower than human-to-human transmission.

2018 Undergraduate Research Program
[Mostly supported by a separate NSF-REU grant]
(June 11 - August 9, 2018)

The goal of this MBI NSF-funded program is to introduce students to exciting new areas of mathematical biology, to involve them in collaborative research with their peers and faculty mentors, and to increase their interest in mathematical biology. The program consists of three parts - each including a mix of educational and social experiences:

- **Introduction to Mathematical Biosciences** (June 11th-15th, 2018) at the MBI
  At the MBI, participants are introduced to various areas of mathematical biology via lectures and computer labs and visit various biological labs on campus.

- **Mentored Research Experience** (June 18th-August 3rd, 2018) at IUPUI, NJIT, or PSU
  During the second component of the program, participants complete a mentored research project individually or in pairs at one of MBI's IP. Participants also attend a weekly online seminar series and virtual all-program meeting.

- **Capstone Conference** (August 6th-9th, 2018) at the MBI
  For the final week of the program, the students return to the MBI to participate in the Capstone Conference. A student-centered conference featuring talks and posters by students doing research in mathematical biology, keynote talks by prominent mathematical biologists, a graduate studies recruitment fair, and other special features including a conference dinner and social event. Note that the Capstone Conference is open to all undergraduate students doing research in the mathematical biosciences, not only to students participating in the MBI REU.

Project Descriptions

Indiana University – Purdue University Indianapolis (IUPUI)
Site Leader: Julia Arciero

- **Project 1**: Using a Mathematical Model to Understand How Pairs of Red Blood Cells Interact in Linear Shear Flow
  Mentor: Dr. Jared Barber
  Description: Blood is composed of mainly red blood cells (45%) and plasma. As blood flows through vessels, cells near walls are pushed towards the vessel center by wall interactions but pushed away from the vessel center by interactions with other cells. These competing effects have a primary role in how cells are distributed across the vessel which, in turn, affect distribution of other important quantities like oxygen. We have developed a two-dimensional computational model of red blood cell motion to investigate how two isolated cells interact near vessel walls. The project will be use a previously-developed model to consider different types of interactions that pairs of cells undergo in this environment, how these interactions affect diffusion and mixing of cells, and the effects of various parameters like cell flexibility and size on these results.

- **Project 2**: Implementation of Advanced Topology Optimization Methods
  Mentor: Dr. Andres Tovar
  Description: In applied mathematics and engineering, topology optimization is known as the most effective material distribution numerical approach for synthesizing structures without any preconceived shape. Currently, a number of topology optimization algorithms

is freely available in Matlab and other programming languages. Most of these algorithms use so-called density-based method, which can be used in 2D and 3D structures. The objective of this work is to implement more advanced topology optimization methods such as the level set-based and/or the phase field-based method. The student participating in this project will gain a complete understanding of the mathematics behind topology optimization and exposed to all related Matlab tools. The result of this research experience is the numerical implementation, analysis, and application of advanced topology optimization methods in structural optimization.

- **Project 3**: Using a Mathematical Model of Sepsis to Predict Survivability Conditions
  Mentor: Dr. Julia Arciero
  Description: Sepsis is a very serious and life-threatening illness caused by the body's response to an infection. Experiments conducted in rats have shown that once a bacteria load exceeds a certain level, the rats do not survive. The presence of bacteria in the blood leads to a significant inflammatory response which in turn causes rapid damage to the body's tissues that triggers a self-sustaining loop of damage and inflammation, eventually leading to either septic (bacteria-driven) or aseptic (inflammation-driven) death. The objective of this study is to use a mathematical model to predict the survivability range for an infection given varying doses or degrees of virulence of a bacterial infection. A model of ordinary differential equations will be used to simulate interacting populations of the bacteria and immune system. Experimental data from rat sepsis studies will be used to estimate several model parameters. The model will be used to predict conditions that lead to disease or health outcomes.

New Jersey Institute of Technology (NJIT)
Site Leader: Simon Garnier

- **Project 1**: Modeling Slime Mold Decision-Making as Systems of Coupled Oscillators
  Mentors: Simon Garnier and Jason Graham
  Description: In a complex and dynamic world, how do you choose the best of multiple options when you do not possess a brain, or even the beginnings of a nervous system? From bacteria and immune cells to fungi and plants, the large majority of living beings face this problem every day. Nevertheless our knowledge of decision-making mechanisms is mostly limited to those of neuronal animals, and in particular vertebrates. The goal of this project is for students to explore with University of Scranton Assistant Professor Jason Graham and NJIT Assistant Professor Simon Garnier the choice-making abilities of a non-neuronal model organism: the slime mold Physarum polycephalum. Using models of coupled oscillators, the students will study the integration of noisy and contradictory information and the role of memory during decision-making by P. polycephalum. They will also compare their results to experimental data collected by Garnier's lab as part of an IOS NSF-funded research effort. The results of this work will help understand information processing in organisms without a brain, thereby advancing our comprehension of the emergence of cognitive processes in biological systems.

- **Project 2**: Emergent oscillations in electrically coupled neuronal networks
  Mentors: Jorge Golowasch and Farzan Nadim

Description: Electrical coupling of neurons via gap junctions can produce network oscillatory activity in the absence of any oscillatory components. Such oscillations depend on network activity spreading through closed loops (re-entry) through which action potentials can spread, thus producing periodic potential firing patterns of the component neurons (Gansert et al, 2007, J. Neurophysiol). The properties of these re-entrant loops and the types of activity they can generate are mostly unknown. This project will combine computational modeling and mathematical analysis to characterize the types of activities that such networks can produce. Specific questions that will be addressed are: 1) What role does the size of the network play in the activity generated; 2) What is the role of electrical coupling strength; 3) What is the network output capacity; 4) How do intrinsic properties of neurons, specifically membrane potential resonance, influence network output.

Penn State University (PSU)
Site Leader: Dennis Pearl

- **Project 1**: Assessing the Value of ChIP Data
  Mentor: Qunhua Li
  Description: ChIP-exo is a high-throughput technology for identifying protein binding sites on DNA. It has near single-bp resolution, providing detailed structural information on the organization of protein-DNA complexes at a fine scale. However, robust measures for assessing its quality and reproducibility are still lacking. While there are quality measures for similar but lower-resolution technologies, such as ChIP-seq data, these measures do not work well for ChIP-exo due to its high resolution. This project aims to use machine learning techniques to build a predictive model for automatically classify quality and reproducibility of ChIP-exo experiments and extract predictive features.

- **Project 2**: Space-Time Models for Infectious Diseases
  Mentor: Murali Haran
  Description: Space-time models for infectious diseases: Infectious diseases like rotavirus, pertussis, measles, and meningitis have a major impact on populations all over the world, particularly on children in sub-Saharan Africa. These disease present a number of important challenges including estimating the current burden and anticipating the future burden of these diseases, as well as studying the impact of different vaccination strategies on controlling their spread. These research problems involve developing models for the diseases and combining disparate sources of information such as surveillance data and hospital records. In these projects students will be introduced to infectious disease modeling via susceptible-infected-recovered (SIR) models. They will learn simulation techniques, as well as estimation and computational methods for fitting these models to data, both via maximum likelihood and Bayesian methods. They will learn these methods through simulated examples and by applying them to real data sets obtained from collaborators at the Center for Infectious Disease Dynamics (CIDD) at Penn State.

- **Project 3**: Nonparametric Models for Animal Movement
  Mentor: Ephraim Hanks
  Description: Movement is a fundamental process underlying the spread of infectious disease, the spread of invasive species, and the flow of information and resources in social species. Understanding and predicting realistic movement of humans and animals can lead

to improved surveillance of disease and more accurate predictions of the effects of changing landscapes. Animal movement is highly complex, exhibiting dependence in time, correlation in movements between conspecifics, changing behavior across seasons, hard constraints such as rivers and cliffs, and response to local environmental cues. Current statistical models for animal movement fail to capture this complexity fully. Based on Taken's theorem (Taken 1981), complex dynamical systems such as animal movement can often be well-represented by a lower-dimensional dynamical system, and the dynamics are often captured well by considering lagged time observations of the system. This suggests a nonparametric approach for modeling movement based on (1) the current local environment, (2) the animal's current movement state, and (3) the animal's state at multiple previous time steps. In this project, students will use modern machine learning approaches to build models that capture and replicate the complexity of animal movement, and will apply these models to various animal systems, including social movements of ants in a nest, sea lion foraging trips, and elk migrations.

- **Project 4**: Estimating the Distribution of Amino Acids in the Pre-biotic Period
  Mentor: Dennis Pearl
  Description: Estimating the Distribution of Amino Acids in the Pre-biotic period. When reconstructing phylogenetic histories from highly conserved sequences in all domains of life, recent evidence in several ancient enzymes shows that the distribution of amino acids is different at the root of the "tree of life" than in more rapidly changing newer enzymes. This provides a signal for the distribution of amino acids associated with a pre-biotic era (Pollack et al., 2013). In this project students will develop estimates of the pre-biotic distribution of amino acids from a variety of perspectives and combine evidence from phylogenetic and laboratory assessments. They will also develop and apply a new model of molecular evolution that allows for the amino acid distribution to vary with the level of site conservation. Students will advance their knowledge of stochastic evolutionary processes, and become skilled in aspects of probability and statistic inference associated with their use.

Students, Mentors and Projects

Name	REU	Project	Mentor
Torsey, Allison	IUPUI	Using a Mathematical Model of Sepsis to Predict Survivability Conditions	Julia Arciero
Carpenter, Amy	IUPUI	Using a Mathematical Model of Sepsis to Predict Survivability Conditions	Julia Arciero
Kardadi, Sophia	IUPUI	Implementation of Advanced Topology Optimization Methods	Andres Tovar
Amran, Maryam	IUPUI	Using a Mathematical Model to Understand How Pairs of Red Blood Cells Interact in Linear Shear Flow	Jared Barber
Haslam, Alanna	NJIT	Modeling Slime Mold Decision-Making as Systems of Coupled Oscillators	Simon Garnier and Jason Graham
Dribki, Yassine	NJIT	Modeling Slime Mold Decision-Making as Systems of Coupled Oscillators	Simon Garnier and Jason Graham
Cheng, Susan	NJIT	Emergent Oscillations in Electrically Coupled Neuronal Networks	Farzan Nadim and Horacio Rotstein
Morrison, Maike	PSU	Assessing the Value of ChIP Data	Ephraim Hanks and Murali Haran
Strong, Emily	PSU	Assessing the Value of ChIP Data	Ephraim Hanks and Murali Haran
Brown, Benjamin	PSU	Assessing the Value of ChIP Data	Qunhua Li

MBI POSTDOCTORAL TRAINING

The goal of the MBI Postdoctoral Fellow program is to produce scientists with an independent research program; the MBI mentoring program is aimed at helping to accomplish this goal. The MBI training program prepares postdoctoral fellows for jobs in university or college teaching, industry, and national labs. The MBI mentoring program has a number of distinctive features.

1) Each postdoctoral fellow has two designated scientific mentors: one in the mathematical sciences and one in the biosciences. The scientific mentors serve as senior collaborators who facilitate the scientific progress of the post-docs, as well as serve as professional mentors and role models. The scientific mentors are chosen in cooperation with the Directorate and the mentors may change from time to time.
2) MBI approved scientific mentors are researchers at either Ohio State or at one of the MBI Institute Partners; MBI funds face-to-face contacts with external mentors.
3) Each postdoctoral fellow receives $2,500 per year for professional travel. These funds facilitate professional development by supporting their participation in professional meetings or their travel to work with collaborators other than the designated mentors.
4) A unique feature of the MBI postdoctoral fellow experience is the networking capabilities afforded to each post-doc because of the large number of MBI visitors. We set up opportunities for the post-docs to interact with many of our visitors.
5) To support self-reflection and oversight by the MBI director, each post-doc writes an annual report describing his or her accomplishments of the previous year and his or her expectations for the next year. The reports are reviewed in a formal meeting with two members of the Directorate.
6) To foster collaboration and offer opportunities to practice presentations of different types, each MBI post-doc gives (at least) one scientific talk each year in the Post-Doc Seminar and poster presentations at the annual Institute Partner Meeting and the annual Scientific Advisory Committee Meeting.
7) Each MBI postdoctoral fellow is encouraged to teach one course while at MBI. MBI has arrangements with the Mathematics Department to make this possible; opportunities in other departments are handled on a case-by-case basis. Post-docs are observed and provided with teaching feedback and coaching by departmental faculty or MBI directors.
8) MBI postdoctoral fellows are encouraged to participate as mentors in the MBI graduate and undergraduate summer schools; some post-docs participate as mentors for Ohio State undergraduate research projects in mathematical biology.
9) The post-docs receive professional mentoring in two ways:
    a. Monthly meetings of the post-docs with Mike Reed (Senior Scientific Advisor) and Tony Nance (Deputy Director). These meetings discuss grant writing, elevator talks, department politics, among many other topics.
    b. In informal discussions with members of the MBI Directorate, MBI visitors, and members of the OSU & national communities.
10) Collectively the post-docs have several responsibilities that allow them to practice their communication and organizational skills.
    a. They help write reports for the MBI scientific workshops (each workshop report is written by a group of three post-docs; each post-doc writes two reports). This activity provides an opportunity to practice writing and summarizing for a broader audience.
    b. MBI postdocs officially represent MBI at SACNAS/MMW, Field of Dreams, and other diversity oriented events

c. Two MBI postdocs co-organize the MBI Postdoc Seminar Series, a weekly series that takes place in non-workshop weeks
d. One post-doc co-organizes the monthly Professional Development Seminar with Mike Reed and Tony Nance. That postdoc also works with Tony to organize professional Development events that occur between the monthly meetings.

MBI Postdoctoral Fellows

MBI NSF Supported Postdoctoral Fellows 2017-18 (bold = leaving MBI)

1. Amir Asiaee Taheri (Computer Science, University of Minnesota)
2. Veronica Ciocanel
3. Punit Gandhi
4. Colin Klaus
5. Colby Long
6. **Reginal McGee**
7. Inom Mirzaev
8. **Farrah Sadre-Marandi**
9. Omar Saucedo
10. Alexandria Volkening
11. Yangyang Wang

MBI Postdoctoral Fellow Hires to start in 2018

1. Anastasios Stefanou
2. Celeste Vellejo
3. Waisur KhudaBukhsh

Post-doc Professional Development Seminar:

This monthly meeting, led by **Mike Reed** and **Tony Nance,** gave postdoctoral fellows the chance to practice talks of all descriptions and to discuss career-related issues (such as grant writing, job application material, networking, etc.).

Post-doc Seminar Series:

1. September 21, 2017, Farrah Sadre-Marandi (Mathematical Biosciences Institute)
   Gender differences in hepatic one-carbon metabolism
   https://mbi.osu.edu/event/?id=1180

2. September 28, 2017, Omar Saucedo (Mathematical Biosciences Institute)
   Spatial Dynamics of Vector-Borne Diseases
   https://mbi.osu.edu/event/?id=1181

3. October 26, 2017, Ben Fogelson (Mathematical Biosciences Institute)
   Mechanics of nuclear pore transport
   https://mbi.osu.edu/event/?id=1182

4. November 9, 2017, Yangyang Wang (Mathematical Biosciences Institute)
   Piecewise smooth models of a biological motor control system
   https://mbi.osu.edu/event/?id=1183

5. November 30, 2017, Reginald McGee (Mathematical Biosciences Institute)
   A Bundled Solution for High-Dimensional Informatics Problems
   https://mbi.osu.edu/event/?id=1184

6. December 7, 2017, Punit Gandhi (Mathematical Biosciences Institute)
   Water Transport in Dryland Ecosystems: Shaping Banded Vegetation Patterns
   https://mbi.osu.edu/event/?id=1185

7. January 25, 2018, Alexandria Volkening (Mathematical Biosciences Institute)
   Modeling pattern formation on zebrafish
   https://mbi.osu.edu/event/?id=1187

8. February 1, 2018, Veronica Ciocanel (Mathematical Biosciences Institute)
   Modeling mRNA Localization: Insights from Including the Microtubule Cytoskeleton
   https://mbi.osu.edu/event/?id=1188

9. February 8, 2018, Inom Mirzaev (Mathematical Biosciences Institute)
   Analytical and Numerical Investigation of Long-term Behavior of Microbial Flocculation Equations
   https://mbi.osu.edu/event/?id=1189

10. February 15, 2018, Colin Klaus (Mathematical Biosciences Institute)
    Visual Transduction: A Signaling Paradigm Across Scale Orders
    https://mbi.osu.edu/event/?id=1214

11. March 1, 2018, Amir Asiaee T. (Mathematical Biosciences Institute)
    Generalized High Dimensional Data Sharing with Application in Uplift Detection of Cancer Treatments
    https://mbi.osu.edu/event/?id=1190

12. March 22, 2018, Xiulan Lai (Mathematical Biosciences Institute)
    A stochastic model of axonal organelle accumulation induced by reduction of molecular motors
    https://mbi.osu.edu/event/?id=1191

13. April 5, 2018, Colby Long (Mathematical Biosciences Institute)
    Rank Conditions for Phylogenetic Inference
    https://mbi.osu.edu/event/?id=1215

EARLY CAREER AWARDS

ECA are competitively awarded annually by MBI to enable tenure-track faculty to participate in MBI emphasis programs by **spending three-four months in residence at MBI.** The annual ECA awards were as follows

- David Murrugarra – University of Kentucky, September 2017 – November 2017
- Calistus Ngonghala – University of Florida, January 2018 – May 2018

- Megan Powell – University of St. Francis, January 2018 – May 2018
- Daniel Linder – Augusta University, January 2018 – May 2018

LONG TERM VISITORS

- Fernando Antoneli - Universidade Federal De São Paulo, February 2018 - March 2018
- Graham Donovan - University of Auckland, September 2017 - October 2017
- Léo Girardin - Université Pierre et Marie Curie, September 2017 - December 2017
- Xiulan Lai - Renmin University of China, September 2016 - August 2018
- Kang-Ling Liao - The Ohio State University, January 2018 - February 2018
- Maciej Pietrzak – The Ohio State University College, June 2017 - December 2017
- Claire Postlethwaite - University of Auckland, September 2017 - October 2017
- Pamela Pyzza - Ohio Wesleyan University, January 2018 - March 2018
- Leili Shahriyari - The Ohio State University, September 2017 - December 2017
- Piotr Sliwka - Cardinal Stefan Wyszynski University, September 2017 - November 2017
- Diana Steele - National Association of Science Writers, August 2017 - December 2017
- Peter Thomas - Case Western Reserve University, August 2017 - December 2017
- Martin Wechselberger - University of Sydney, August 2017 - September 2017
- Yi-yi Zhu - Shanghai Municipal Center for Disease Control & Prevention (SCDC), September 2017 - October 2017
- Boseung Choi - Daegu University, February 2018
- Jacek Wesolowski - Warsaw University of Technology, March 2018
- Yangjin Kim – Konkuk University, July 2018 – August 2018, July 2018 – August 2018
- Ben Fogelson – University of Utah, September 2017 – November 2017 (co-sponsored Post-Doctoral Fellow).
- Daniele Cappelletti – University of Wisconsin, May 2018
- Nourridine Siewe – NimBios, August 2017
- Moise Nicolae - Carol Davila University of Medicine and Pharmacy, August 2017 – September 2017

Long Term Visitors currently expected for 2018-2019

- Hsiu-Chuan Wei – Feng-Chai University, August 2018 – July 2019
- Fengzhu Xiong – Brigham Womans Hospital – September 2018 – October 2018
- Min Yang – Oklahoma State University, Spring 2019
- Bill Holmes – Vanderbilt University, Spring 2019
- Hidir Nogay - Erciyes University, August 2018 – August 2019

VISITOR REPORTS (LONG TERM VISITORS AND EARLY CAREER AWARDEES)

Yangjin Kim
Konkuk University
The purpose of trip to MBI was to do research collaboration with Prof. Avner Friedman and experimentalists including Profs. Balveen Kaur and Ji Young Yoo at Department of Neurosurgery, attending workshops at the MBI, interacting with MBI postdocs and visitors for research activities.

Here are a list of workshops that I attended/participated in, talks I gave and other activities I joined in while at MBI:

MBI Workshops attended
Workshop 1: The biological challenges in morphogenesis
Workshop 2: Modelling of tissue growth and form
Workshop 3: Hybrid multi-scale modellling and validation

Talks given
1. "The role of microenvironment (M1/M2 macrophages) in regulation of cell infiltration in glioblastoma", MBI visitor seminar, Mathematical Biosciences Institute (May 1, 2017).
2. "Mathematical modeling of tumor growth: hybrid approaches", Applied Math Seminar, Dept of Mathematics, Ohio State University (USA, Apr 13, 2017).

Other activities
1. Attended MBI national colloquium (Leah Edelstein-Keshet (Jan, 2017), Phillip Maini (Jan, 2017)

The research I worked on while at MBI was working on Bortezomib, a peptide-based, reversible proteasome inhibitor, has been shown to induce a synergetic effect on cancer cells killing in OV therapy. In this paper, we demonstrate that NK cells play a dual role in cancer cells killing in OV therapy, using a combination of a mathematical model and in vivo experiments. Using a GFP analysis, we show that depletion of endogenous NK cells significantly increased anti-cancer efficacy of many GBM cells. Based on these experimental data, we developed a partial differential equation model of NK cells effects on tumor cell killing in combination treatment with bortezomib and OV therapy, which we used to generate mechanistic hypotheses. The mathematical model predictions revealed that endogenous and exo- NK cells may play a critical role in modulating this tumor cell killing property, which was supported by experimental data using quantitative GFP(+/-) analysis. These results suggest that in addition to their classical role as immune cells, NK cells plays a dual role in modulating replication of oncolytic viruses and its elimination, and combination of OV-induced apoptosis, bortezomib-induced necroptotic cell death, and adjuvant NK cell treatments has to be well-balanced.
The following are publications that I worked on/completed while at MBI
1. Yangjin Kim, Ji Young Yoo, Balveen Kaur and Avner Friedman, Complex Role of NK cells in regulation of OV-Bortezomib therapy, Proc Natl Acad Sci USA, Aug, 2017, submitted, Aug 29, 2017.
2. Yangjin Kim, Ji Young Yoo, Balveen Kaur and Avner Friedman, Dynamics of M1 and M2 microglia on tumor cell killing: a mathematical model, to be submitted to J. Royal Society Interface, 2017.
3. Yangjin Kim, Hyunji Kang, Gibin Powathil, Hyeongi Kim, Dumitru Trucu, Wanho Lee, Sean Lawler, and Mark Chaplain, Mechanism of glioma invasion: A new strategy to overcome BV normalization failure using astrocytes wall, to be submitted to PLoS One, 2017.
4. Yangjin Kim, The role of the microenvironment in the regulation of cell infiltration in glioblastoma: A hybrid modelling approach, to submitted to PLoS One, 2017.
5. Yangjin Kim, Sean Lawler, Wanho Lee, Sookkyung Lim, and Mark Chaplain, The role of microenvironment in regulation of cell infiltration in glioblastoma, book chapter, "Cell

Movement: Modeling and Applications", Springer, to be submitted, 2017.

Second Visit
Collaborators = Professor Avner Friedman (MBI), professor Jinhua Yu (OSU), professors Balveen Kaur (U of Texas-Houston), Ji Young Yoo (U of Texas-Houston)

During this stay, I collaborated with professor Avner Friedman for several research projects including oncolytic virus therapy on cancer. Oncolytic viruses such as herpes simplex virus-1 (oHSV) are genetically modified to target and kill cancer cells while not harming healthy normal cells and are currently under multiple clinical trials for safety and efficacy. Bortezomib is a peptide-based proteasome inhibitor and is an FDAapproved drug for myeloma and mantle cell lymphoma. Our research collaboration with Balveen Kaur group at Comprehensive Cancer Center at Ohio State University on OV-bortezomib-NK therapy in glioma therapy resulted in a publication in a prominent journal, PNAS:
Yangjin Kim, Ji Young Yoo, Tae Jin Lee, Joseph Liu, Jianhua Yu, Michael A Caligiuri, Balveen Kaur, and Avner Friedman, Complex Role of NK cells in regulation of OV-Bortezomib therapy, Proc Natl Acad Sci,, 201715295, published ahead of print April 23, 2018.

In the paper we investigated the role of NK cells in combination therapy with oncolytic virus (OV) and bortezomib. NK cells display rapid and potent immunity to metastasis and hematological cancers, and they overcome immunosuppressive effects of tumour microenvironment. We developed a mathematical model, a system of PDEs, in order to address the question of how the density of NK cells affects the growth of the tumour. We found that the anti-tumour efficacy increases when the endogenous NKs are depleted, and also when exogenous NK cells are injected into the tumour. These predictions were validated by our in vivo and in vitro experiments.

Now, the Balveen group moved to University of Texas-Houston Medical Center but we continues to collaborate with this experimental group for another critical study: critical role of M1 and M2 phenotypic switches in regulation of OV therapy. Experimentalists believe that the M1 phenotype infiltrates the tumor in response to OV therapy in the early state of tumor development but these M1 macrophages are cleared away as soon as OVs are cleared away around 15 days of injection. These M1 macrophages critically attack and kill uninfected tumor cells, therefore, lowering the OV anti-tumor efficacy. The critical switch to M2 macrophages will determine the overall anti-tumor efficacy. We had research meeting several times including August 13, 14 and the experimentalists will do PCR to clarify the phenotypic changes. We are developing a mathematical model based on these assumptions which consist of a set of partial differential equations (PDEs) with free boundary.

We also had research meeting (July 30, 2018) with professor Jinhua Yu at internal medicine, School of Medicine at OSU for an interesting research projects on NK cells. NK cells are known to be a first line of defense in response to any attacks and are capable of killing many cancer cells. However, in several experimental studies, it is now known that under certain conditions, these NK cells can actually promote the tumor growth. For example, in STAT5 deficient mice, Bcl-2 within the NK cells, an anti-apoptotic gene, is upregulated, rescuing the NK cells from the programmed cell death, and these can stimulate the high level of VEGFA secretion from NK cells. These VEGFA, an angiogenic factor, then promote the tumor angiogenesis, therefore, tumor growth. Nobody ever studied this problem from mathematical modeling point of view. These experimental

results also highlight the importance of dual role of NK cells in tumor promotion or inhibition. We are developing a PDE-based mathematical model with an aim that understanding of fundamental process of this complex role of NK cells in tumor growth will enhance novel therapeutic strategies.

Boseung Choi
Korea University Sejong Campus, Sejong, South Korea

I have visited MBI during 17 Jul. 2017 ~ 13 Aug. 2017 as a short term visitor of MBI. From 2014, I visited MBI several times. I think that the MBI is the best research institute for collaborating Statistics, Applied Mathematics, and Health sciences (including life sciences and Bio sciences). At the MBI, I have a lot of chances to contact several researcher from the U.S as well as the other countries. I also visited the MBI from South Korea. My objective of visiting the MBI for me is to continue my research. Generally I started new project and sometimes finished the former research at the MBI. The facilities of the institute are well equipped to conduct individual research or collaborative research, and the staff of the institute are well trained to support these studies and their services are very fast and friendly.
For this visiting, I don't attend any workshop because only summer REU program and undergraduate capstone conference are held during my visiting. Two programs are for the undergraduate students. However, I can support a student who attended REU program and capstone conference.

Research and collaborations I worked on while at MBI include:

1. Statistical modelling of the spread of Ebola virus – with Grezegorz Rempala (MBI director), Omar Saucedo (Postdoc of MBI), and Sydney Busch (REU attendee student). The random graphs can be served as models for social networks. In a random graph, individuals in a population are represented by vertices and transmission links between vertices are represented using edges. We applied the random graph method to disease spread modeling. The disease spreads can be modeled using random graph model along the social network obtained. In order to model the spread of Ebola virus in a small town in Republic of Congo, we utilized the random graph model. We also utilized Markov Chain Monte Carlo approach for the Bayesian estimation model.
2. A study to identify the relationship between the occurrence of chlorophyll in a rake or river and liver disease – with Jiyoung Lee (Associate professor of Environmental Health Sciences). The concentration of chlorophyll measured in lakes and rivers is a tool to measure the extent of the algal phenomenon and can have an adverse effect on people who drink chlorophyll contaminated water. Especially liver related diseases can be increased. This research utilized several statistical model including random effect model and cross sectional time series model
3. A study of model efficiency between full model and reduced model of stochastic enzyme kinetics - With Grezegorz Rempala. This study is an extension of the research that was carried out at the last visiting. We have conducted a comparative study of the full model for enzyme kinetics and the reduced forms of SQSSA and TQSSA model. This study focused on the model efficiency of reduced model to the full model.

List of publications that I have submitted or completed.

1. Modeling household transmission dynamics: Application to Diarrheal disease in sub-Saharan Africa, Plos One, submitted.

2. Beyond Michaelis-Menten: accurate and efficient estimation of enzyme kinetic parameters, submitted
3. Schwartz, E., Choi, B., and Rempala, A. (2015). Estimating epidemic parameters: Application to H1N1 pandemic data, Mathematical Biosciences, 270, 198-203.

Nourridine Siewe
University of Tennessee National Institute for Mathematical and Biological Synthesis (NIMBioS)
Purpose of Visit to MBI and nature of work: Short term research visit

- Research with Prof. Avner Friedman on "Chronic Hepatitis B Virus and Liver Fibrosis: A Mathematical Model". An article with the same title was submitted to PloS ONE for publication, and is under review.

- Research with Prof. Avner Friedman on "The Role of Macrophage Migration Inhibitory Factor (MIF) in Severe Malarial Anemia (SMA): A Mathematical Model"; an ongoing project.

Benjamin Fogelson
University of Utah
The purpose of this visit to MBI was to attend the workshops on control in biology and medicine as well as to interact with MBI faculty and postdocs in order to share recent research results and to participate in postdoctoral professional development activities.

Events attended: Workshops 1, 2, and 3 of the Control in Biology and Medicine Emphasis Program.
Presentations given: Modeling the mechanics of transport through the nuclear pore. Hour-long seminar, 26 October 2017.

Any products that were or will be a result of your stay in MBI (please list anything you find applicable here)
- Research
    - Feedback by MBI members on research into the biophysics of nuclear pore transport (especially comments by Adriana Dawes) open new avenues for research.

Yiyi Zhu
Shanghai Municipal Center for Disease Control and Prevention
I am planning to visit MBI for the purpose of learning mathematical modelling in infectious diseases. My work in Shanghai CDC is mainly about surveillance and investigation for acute infectious disease control and prevention. I collected data from daily work and I am exploring simple modelling applications in my work. I searched online and found experts of mathematical modelling in MBI of the Ohio State University. In addition, various workshops and lectures on modelling are held here on each semester, so I will have the opportunities to follow up with the latest findings.

I arrived on September 10, 2017 and began to work and participate in MBI seminars and activities since September 11.

I attended the following workshops and lectures:

1. Emphasis workshop of control and modulation of neuronal and motor system. (September 11-15, 2017).
2. Emphasis workshop of control of cellular and molecular systems. (October 2-6, 2017).
3. Lang Li (Ohio State University). Drug interaction research: translation between EMR data mining and pharmacokinetics modelling. (September 15, 2017 1 PM-2:00 PM)
4. Synthetic biology: life redesigned James Collins (Department of biological engineering, Massachusetts Institute of Technology)(September 20, 2017 12:00 PM - 1:00 PM)
5. Arturo Zychlinsky (Max Planck Institute for Infection Biology). Neutrophils are the effectors of the innate immune system.(October 6, 2017 12:00 PM-1:00 PM)

I also participated in lectures delivered by MBI visitors and postdoc fellows.

1. Yihan Sui (Ohio State University). Spatial model for Pertussis in US.(September 18, 2017 9:15 AM-11:45 AM)
2. David Murrugarra (University of Kentucky). A near-optimal control for stochastic gene regulatory networks. (September 19, 2017 10:20 AM - 11:10 AM)
3. Farrah Sadre-Marandi (Ohio State University). Gender differences in hepatic one-carbon metabolism. (September 21, 2017 10:20 AM - 11:10 AM)
4. Claire Postlethwaite (University of Auckland). Spirals and heteroclinic cycles in rock-paper-scissors. (September 26, 2017 10:20 AM - 11:10 AM)
5. Omar Saucedo (Ohio State University). Spatial dynamics of vector-borne diseases. (September 28, 2017 10:20 AM - 11:10 AM)
6. Eshel Faraggi (Research and information systems, LLC). Intelligent global protein scoring functions. (September 29, 2017 10:20 AM - 11:10 AM)
7. Graham Donovan (University of Auckland). Clustered ventilation defects in asthma. (October 10, 2017 10:20 AM - 11:10 AM)

On October 9, I gave a talk in MBI conference room on Shanghai surveillance and infectious disease control and prevention. I introduced about Shanghai infectious surveillance, including notifiable infectious diseases and syndromic surveillance. I also gave some examples on dengue outbreak, H7N9 and SFTS clusters in China. Director Greg Rempala, Professor Joe Tien and Laura Pomeroy gave inspiring suggestions on possible modeling exploration.

During my stay in MBI, I summarized epidemic data on vomiting and diarrhea, H7N9 and severe fever with thrombocytopenia syndrome. I also collected data on dengue. A case report of Q fever in Shanghai was drafted. I simulated the norovirus reports with temperature with SIR model. I am planning on modeling on infectious disease outbreak and cluster data. Meanwhile, I talked with professor Tien and Pomeroy. SIR models, agent-based models and Markov chain methods was proposed as the tools to study dynamics of infectious disease in my research. Human to human transmission and exposure to environments might be distinguished by mathematical modeling. Birth rate and cross immunity might play a role in infectious disease seasonal fluctuation. I expected to collaborate with them and do future research according to the above advice. Suggestions from Postdoc Omar Saucedo were also very helpful. I am interested in the topic of Infectious Diseases: Data, Modeling, Decisions during 2018 spring emphasis semester and I will watch all the online videos at that time.

I joined in the course of modeling infectious disease in animals and humans. I systematically learned and reviewed on basic SIR Model, control of infectious diseases, host and environmental heterogeneity, simulation and data fitting, agent-based models. Besides, I had sit in the linear algebra and differential equation class. They are all helpful for further mathematical modelling for infectious disease.

I would like to appreciate MBI Directors, professors, postdoc fellows, visitors. Thanks for all the generous help from MBI work staff.

Piotr Śliwka
Cardinal Stefan Wyszynski University in Warsaw
From Sep 28 to Nov 3 I was a visitor in MBI. My main duty is statistical data analysis. I`ve chosen MBI because of similar research done here. For some time I have been working mainly with bioinformatics, psychologists and actuaries in the field of statistical data analysis (including Markov Chains). My recent studies has focused first on the statistical evaluation of the effectiveness of the therapeutic process in the time and secondly on the proposition of the new approach to the estimation of the human mortality rates.

In the first case evaluation of the effectiveness of the therapeutic process is usually accomplished using commonly adapted measures based on appropriate psychological questionnaires. The basic problem, however, is that these measures are static, do not work over time, and therefore do not allow predict in the future the efficiency of the therapeutic process. We propose a new measures based on the second largest eigenvalue and stationary distribution of Markov chains transition matrix. We assume that the patient's responses can be identified with a discrete random variable X_t which takes values from a finite set S, which is additionally a ordinal variable. Values of X_t can be assigned to the states of the Markov chain. If the Markov property is satisfied, $P(X_t = s_i \mid X_{t-1} = s_{j1}) = P(X_t = s_i \mid X_{t-1} = s_{j1}, X_{t-2} = s_{j2},\ldots,X_0 = s_{jk})$, where $s_{jk} \in S$ – set of states, then the effectiveness of the therapeutic process can be sought on the well-known theory of finite Markov chains. The use of Markov chains in the Outcome Questionnaire (OQ-45), which is the fourth most widely used questionnaire for assessment of the therapeutic process, based on Polish and U.S. patients groups is presented in [1] and [2]. Unfortunately, classical Markov property is not always fulfilled. If the therapeutic process is successful, it should bring about an improvement in the health of the patient. Therefore, it would probably be advisable to consider using the higher order Markov chains. The preliminary investigations done in MBI confirm this approach.

In the second case, we propose a new approach to the estimation of the mortality rates based on two models: the first one with colored excitations modeled by Gaussian linear filters (GLSF) and the second one with excitations modeled by continuous non-Gaussian process (nGLSF). The exact analytical formulas for theoretical mortality rates based on GLSF and nGLSF models as well as comparison of the theoretical values obtained in both cases with theoretical mortality rates based on a classical Lee-Carter model were included in [3]. The point and interval forecast (in particular using FanCharts) as well as preliminary work to designate random switching points in MBI was done.

During my stay in MBI in Columbus I`ve participated in two workshops: „Control of Cellular and Molecular Systems" (Oct 2 – Oct 6) and „ Control of Disease: Personalized Medicine Across Heterogeneous Populations" (Oct 30 – Nov 3). In the second case I`ve prepared poster „The Gaussian and non Gaussian Linear Scalar Filter Model for Mortality Rates", based on results

described above. I`ve also gave a talk titled „Markov chains as a tool in statistical data analysis" at the MBI Visitors Seminars. This talk was based on the results included in [1]-[3].

At MBI I`ve started with a new project called „Identification of leukocyte subpopulations based on RNA signature" in collaboration with Maciej Pietrzak (MBI). Our goal will be to propose mathematical and statistical methods to identify the cell type based on the information in the common gene pool.

I rate my visit to MBI as a fruitful time for scientific discussions with the workshop participants and the MBI staff. Highly efficient administration and accommodation service also deserves a high rating.

Literature:
[1] Śliwka P, Simon W., "Markov Chains as a Tool Measuring Effectiveness of a Psychotherapy Process", BIOMAT 2014-International Symposium on Mathematical and Computational Biology, 232-244, 2015;
[2] Simon W., Śliwka P., Sobański J.A., Klasa K., Sala P., Żak W., Busath G., Lambert M.J. "The orthogonal-oblique bi-level model of the Outcome Questionnaire (OQ-45.2) – The case of the Polish factorial normalization", Psychiatria Polska, Vol. 49, 5, 2015.
[3] Śliwka P., Socha L., "A Proposition of Generalized Stochastic Milevsky-Promislov Mortality Models", Scandinavian Actuarial Journal, 2017, in review.

Martin Wechselberger
University of Sydney
The prpose of my visit to MBI was to learn about "Control in Biology and Medicine" (emphasis semester)

I participated in the workshop "Control and Modulation of Neuronal and Motor Systems" (September 11-15).

I gave a visitor seminar (September 8) and presented at the above mentioned workshop (September 13). Title of presentation: "Two-stroke Oscillators"

While visiting the MBI for 3 weeks, I had research interaction/discussion with Marty Golubitsky, Peter Thomas (visitor) and Punit Ghandi (postdoc).

I also had discussions/meetings regarding MBI involvement at SMB 2018 (to be held in Sydney) with Greg Rampala, Janet Best and Adriana Dawes.

Graham Donovan
University of Auckland
I visited the MBI as part of my sabbatical in order to explore new research projects with both other visitors to the MBI, and the MBI postdocs and staff.
During my visit, I attended numerous MBI seminars and workshop talks, and also gave a talk ("Clustered ventilation defects in asthma") on Oct 10, 2017. I also had useful discussions with several people regarding possible research projects, in particular with Marty Golubitsky and Yangyang Wang regarding numerical methods for finding infinitesimal homeostasis, and with

Greg Rempala about a statistical approach to clustered ventilation defects. I hope that both of these will eventually lead to publications. I also had conversations with several other people during the course of my visit which may eventually develop into projects.
On the whole I consider my visit to the MBI very successful, and I am grateful to the institute for its hospitality.

Claire Postlethwaite
University of Auckland
During the period July-Dec 2017, I was on Research and Study leave (also known as sabbatical) from the University of Auckland. As part of my time spent away from Auckland, I visited the MBI, partly to work with Prof Marty Golubitsky to continue projects regarding the dynamics of networks, and partly because the MBI is a stimulating environment for mathematical biologists and I was interested to learn about the work that other researchers were doing. I talked with a number of other researchers, in particular, postdocs Dr Punit Gandhi and Dr Yangyang Wang, as well as Prof Peter Thomas.

I gave a presentation "Spirals and Heteroclinic Networks in Rock-Paper-Scissors" in the visitor seminar series. I attended various other presentations in Visitor Series, the Postdoc Series, and the "Control of Cellular and Molecular Systems" workshop.

My research project with Prof Golubitsky will no doubt result in a publication, but we are still in the process of formulating our results. My discussions with Prof Thomas are relevant to research projects I am currently working on with several graduate students at the University of Auckland, and have the potential to develop into new collaborations.

David Murrugarra
University of Kentucky
I was interested in the emphasis program of fall 2017, which was in Control in Biology and Medicine, as my research interests were directly in line with this topic. My interest in the MBI Early Career Award was the research and networking opportunities at the institute. I expected that my background on modeling biological systems using discrete approaches would complement the expertise of faculty, postdocs, and other visitors at the institute providing participants with a richer spectrum for potential interactions.

I gave the following contributed talks:

1. A Near-Optimal Control for Stochastic Gene Regulatory Networks, MBI Visitors Seminar, Mathematical Biosciences Institute (MBI), Columbus, Ohio, September 19, 2017.
2. Gene expression analysis in Axolotls, Data Analytics Seminar, MBI, November 6, 2017.

I attended the following workshops of the emphasis semester.

1. Control and Modulation of Neuronal and Motor Systems, Mathematical Biosciences Institute (MBI), Columbus, Ohio, USA, September 11, 2017 - September 15, 2017.
2. Control of Cellular and Molecular Systems, Mathematical Biosciences Institute (MBI), Columbus, Ohio, USA, October 02, 2017 - October 06, 2017.

3. Control of Disease: Personalized Medicine Across Heterogeneous Populations, Mathematical Biosciences Institute (MBI), Columbus, Ohio, USA, October 30, 2017 - November 03, 2017.

Collaborations and interactions while at MBI:
I have informally interacted with some of the postdocs and other visitors at the institute. I have interacted with Ali Foroughipour, a graduate student in the Rempala Lab, on problems related with feature selection from microarray data. I also interacted with MBI visitor Piotr Sliwka on problems related to the convergence of Markov chains.

Research being done while at MBI:
During my stay, I have worked on control of discrete dynamical systems. I expect to publish a paper from this research within the next year. I also developed a new collaboration with a colleague from OSU and expect to write a grant proposal in the future as part of this collaboration.

Miscellaneous: I also enjoyed the different social activities in the institute, especially the Kayaking and the picnic.

Fernando Antoneli Jr.
Universidade Federal de São Paulo (UNIFESP) – São Paulo – Brazil
The Purpose of my visit to Ohio State University (OSU) and MBI was to visit Martin Golubitsky, as part of the OSU – FAPESP joint project "Geometry and dynamics between Ohio and São Paulo", to continue our collaboration on the subject "Network Dynamics".

My stay at MBI – OSU coincided with the thematic program "INFECTIOUS DISEASES: DATA, MODELING, DECISIONS SPRING 2018" and, I attended the "Workshop 1: Host-Pathogen Dynamics" (February 19, 2018 – February 23, 2018) of the aforementioned thematic program.

I presented the seminar "Homeostasis, Singularities and Gene Regulatory Networks" in the MBI Visitors' Seminar of February 27, 2018.

The main objective of my visit was to continue the collaboration with Martin Golubitsky (MBI and Department of Mathematics – OSU). We concluded our first study of the role of homeostasis in the dynamics of networks, and published a paper about expression homeostasis in gene regulatory networks (GNR), which had been initiated when Martin Golubitsky visited us at UNIFESP in June 2017:

- F. Antoneli, M. Golubitsky and I. Stewart, "Homeostasis in a feed forward loop regulatory gene motif network", *J. Theoretical Biology* **445** (2018) 103-109.

In this paper we consider unicellular organisms, and look at genes that exhibits "expression homeostasis", namely, the concentration of the synthesized protein remains approximately constant when other cell inputs vary. Special sub-networks called "motifs" are unusually frequent in networks, suggesting that they might have significant biological function. Potentially, one of these functions is homeostasis. In support of this hypothesis, we show that a motif called "feed-forward loop" is able to display homeostasis robustly. The analysis uses the notion of *infinitesimal homeostasis*, which occurs when the input-output mapping has a critical point

(vanishing derivative). This interpretation opens the way for application of methods of *singularity theory* in the analysis of the existence of points of homeostasis and their structural stability. In the case of a feed-forward loop, every external influence on the motif is represented by a single scalar input parameter. We are currently extending the ideas and methods of this paper to treat more complicated motifs, obtained by superimposing two or more feed-forward loops. In these cases the external influence on the motif is reflected by more than one input parameter.

Megan Powell
University of St. Francis, Joliet, IL
Purpose of Visit to MBI and nature of work
The purpose of my visit to MBI was to allow time to focus on research and interact with peers from around the world to develop my research ideas. The majority of my time was spent on my work on modeling inhalation anthrax.

I attended the four emphasis workshops on host-pathogen dynamics, socioepidemiology, disease ecology/eco-epidemiology, and multiscale dynamics of infections. I additionally attended the post-doc, visitor, and online seminars. I gave a talk, Tasmanian devils and devil facial tumor disease discussing the rapid spread of DFTD and potential strategies to save the devil in the wild.

I have submitted the following publications

-Parameter estimation for *in vitro* anthrax studies to Spora

-Creating Undergraduate Research Opportunities Through Interdisciplinary and Intercollegiate Collaboration to the Mathematics Teaching-Research Journal

-How length of possession affects winning probabilities in a shortened NFL overtime to the Journal of Sports Analytics

-A computation framework for inter-species extrapolation for inhaled microbial pathogens to Microbial Risk Analysis

Daniele Cappelletti
University of Wisconsin-Madison
I am a Visiting Assistant Professor at the University of Wisconsin-Madison, and my research focuses on probabilistic models for biochemistry. Hence, visiting the Mathematical Biosciences Institute was certainly interesting to me, as well as learning how it functions.

The main purpose of my visit was to collaborate with Grzergorz Rempala, who is based at the MBI. The visit was very fruitful, as we were able to prove an interesting result which will lead to the submission of a research paper. We are currently preparing the article, and we have weekly meetings via Skype since the time of my visit.

The project we are working on deals with the approximation of the time evolution of a single molecule that undergoes stochastic chemical transformations driven by the present of other molecules, also randomly changing in time. This work has been motivated by the recent ability of biologist to follow the transformations of single molecules in laboratory. Moreover, it fits in a

more vast scenario of approximating the dynamics of large systems of interacting molecules: when many molecules are present, keeping track of the trajectories of all of them is computationally cumbersome. Deterministic solutions of differential equations are used to approximate the average stochastic dynamics, but this technique ignore stochastic fluctuations that are sometimes important to consider. Diffusive models have been proposed to bridge the gap, but these models are only defined up to certain stopping times. The solution we propose is to simulate a certain number of independent approximations of trajectories of single molecules (which is computationally cheap) and to consider their average: by doing so we are able to recover the stochastic fluctuations around the average dynamics, and the simulation can be carried on up to any positive time point. We rigorously prove the convergence of our methods by calculating explicit bounds on the errors.

Léo Girardin
Sorbonne Université, Paris, Laboratoire Jacques-Louis Lions
Collaboration with King-Yeung (Adrian) Lam.

- I gave a talk entitled "Non-cooperative Fisher-KPP systems: traveling waves and long-time behavior" at the PDE Seminar of the Maths Department
- I gave a talk entitled "Non-cooperative Fisher-KPP systems: traveling waves and long-time behavior" at the Visitor Seminar of the MBI
- I attended regularly the PDE Seminar of the Maths Department
- I attended with Pr. Lam an AMS Meeting in Buffalo.

Possible publication

- With Pr. Lam, article entitled "Invasion of an empty habitat by two competitors: spreading properties of monostable two-species competition--diffusion systems", submitted (preprint on arXiv).

Calistus Ngonghala
University of Florida
My work for the Early Career Award involves testing a theoretical model framework I developed with statistical analyses on field data that include health care interventions and to investigate the behavior of the model framework with comprehensive sensitivity analyses and techniques from nonlinear dynamical systems and statistics.

I have also been exploring feedbacks between land-use change, disease, and poverty and attempting to address questions related to sustainable development and ecosystem services.

Additionally, I have been involved in developing a mathematical model to explore the effects of temperature and climate change in general on malaria and Zika virus control programs.

Events attended:
MBI Visitor Seminar.
MBI Workshop on Socio-epidemiology, 03/05-09/2018 (Full participation).
MBI Workshop on Disease Ecology and Eco-epidemiology 03/26-30/2018 (Full participation).
MBI Workshop on Multiscale Dynamics of Infections, 04/23-27/2018 (Attended only a few talks, but interacted with many participants).

Presentations given:

Understanding the ecology of poverty and disease through an integrated ecological-economic framework, Workshop on Disease Ecology and Eco-epidemiology 03/30/2018.
Ecology of poverty and disease: a coupled ecological-economic framework, Workshop on Socio-epidemiology, 03/07/2018.
Rural poverty: a dynamical and ecological perspective, Visitor Seminar, 02/06/2018.

While at the MBI I talked with a number MBI visitors including Professors Avner Friedman, Joe Tien, Ayaz Hyder, and Kesh Govinder and some of these discussions might result in future collaborations. I met and discussed future collaboration plans with MBI workshop participants including Professor Carlos Castillo-Chavez, Suzanne ORegan, Jan Medlock, and Juan Gutierrez. I was opportune to catch up with my postdoctoral mentors (Dr. Matthew Bonds, Professor Suzanne Lenhart, and Dr. Cristina Lanzas), and some colleagues and collaborators including Professor Rohani Pejman, Professor Zhilan Feng, Dr. Nita Bharti, Dr. Benjamin Roche, Dr. Olivia Prosper, Dr. Marisa Eisenberg, Dr. Josephine Kagunda, Dr. Lauren Childs, Dr. Hayriye Gulbudak , and Dr. Chirove Faraimunashe.

While at the MBI I reviewed research articles for four journals: Journal of Theoretical Biology, Journal of Biological Systems, Mathematical Biosciences, and PLoS One.

Because my visit was only been from January 28-May 2018, and because I worked on a number of things at the same time, I was not able to publish or submit any article during the visit. However, I might be submitting two articles from my visit in the summer and more articles resulting from work carried out during the visit will follow in the course of the academic year. The visit has given me an opportunity to gather information and to think about some of the things to include in my Career Grant Proposal and a second grant on the impact of insecticide treated bed-nets on malaria control.

Pamela Pyzza
Ohio Wesleyan University
As a tenure-track faculty member at Ohio Wesleyan University, I am provided the opportunity to take a pre-tenure sabbatical semester. During this sabbatical, faculty are encouraged to spend their time making progress on research that they may not be able to devout as much time to while teaching. While science faculty often travel to work in labs at other institutions during their sabbaticals, my research doesn't require lab amenities, just a capable computer and access to library resources. This gave me the unique opportunity to research in almost any location. Visiting MBI provided me with a physical place to work, but much more importantly, it was a place to collaborate, generate new ideas, and be productive in research endeavors.

In my research, I am primarily interested in creating mathematical models to investigate biological mechanisms, especially in networks that appear in biological systems. Through a combination of agent-based and firing-rate network modeling, I investigate dynamics that are present in neuroscience and epidemiology. I study these models using computational and analytical techniques.

While visiting at MBI, I focused on two research projects. I am collaborating with my coauthors of [1], including MBI co-director, Janet Best, on a second publication. Through our initial work, we have expanded our mathematical model to include additional biological details associated with

human sleep patters and effects of drastic ambient temperatures on the body's ability to maintain a core body temperature. Our second paper focuses on the result that temperature does not only affect one's current night of sleep, but that there is an interaction between temperature effects and prior nights' sleep history that produces the observed sleep and REM—NREM behaviors. A working title for this paper is "Temperature effects interact with sleep history in a mathematical model of sleep regulation". While at MBI, we added simulation results and discussion material to the manuscript and began finalizing the paper. We plan to submit the paper to the Journal of Theoretical Biology.

Based on work done for my dissertation, my collaborators and I are working toward two papers, which highlight different components of our mathematical models that focus on modeling aspects of the insect olfaction process. The first paper focuses on a computational model based on the integrate-and-fire neuron showing similar results and network behavior when compared to models using the more complicated Hodgkin-Huxley neuron. We plan to submit this article to the Journal of Computational Neuroscience. The second paper focuses on the analytical description of a firing-rate model for the locust antennal lobe, which agrees strongly with prior computational work and experimental results. We are still in discussion about the best journal audience for this paper. While at MBI, model parameters were adjusted to adjust to better align model results with biological and experimental details. Further, additional simulations were conducted to fully support the results and conclusions of the network model. Manuscripts for both aspects of the research have been outlined and are expected to be finalized soon.

While at MBI, I attended several Visitor Seminars, Online Mathematical Biology Colloquia, and Postdoctoral Seminars. I gave a presentation titled, Idealized Models of Insect Olfaction, during the Visitor Seminar Series. I also attended several talks during the Host-Pathogen Dynamics and Socioepidemiology workshops. Along with one of the other visiting faculty, we discussed tenure track positions with the MBI postdocs during their Professional Development Seminar. We discussed the interview process as well as many of the day-to-day aspects of a tenure track faculty position involving research, teaching, and service responsibilities. We shared our experiences and advice on topics including helpful inquiries to make during an interview and how to prepare for research talks and mock lectures.

Based on the research discussed above, I expect to submit three publications during the upcoming months.

[1] J. Best, S. Banuelos, G. Huguet, A. Prieto Langarica, P. B. Pyzza, M. H. Schmidt, S. Wilson. "Effects of Thermoregulation on Human Sleep Patterns: A Mathematical Model of Sleep--Wake Cycles with REM--NREM Subcircuit" in Applications of Dynamical Systems in Biology and Medicine, vol. 158, T. Jackson, A. Radunskaya, Eds. New York: Springer, 2015, pp. 123--147.

Peter J. Thomas
Case Western Reserve University

I spent the fall 2017 semester at MBI as Distinguished Scholar in Residence. The purpose of the visit was to participate in the emphasis semester on control theory in biology and medicine, which I helped organize. Along the way I also solicited articles for a special issue of the Springer journal *Biological Cybernetics* on the same topic, organized the visitors' seminar, and worked closely with

postdoctoral scholar Yangyang Wang on a joint research project related to control of motor systems.

I attended all four workshops, many of the visitors' seminars, and three of the postdoctoral seminars. I co-organized the first workshop (control and modulation of neural and motor systems) and had excellent interactions with many workshop attendees all semester. I gave a talk in the third workshop on "Open Versus Closed Loop Control in a Respiratory Model".

Any products that were or will be a result of your stay in MBI (please list anything you find applicable here)

- Research
    - I learned a great deal about control theory in general, and its applications in biology and medicine specifically.
    - I made progress with Yangyang Wang on analysis of nonlinear limit cycle systems with certain kinds of hard/sliding boundary conditions that arise in motor control applications. We have a manuscript in preparation.
    - I discovered a part of nonlinear control theory – called bilinear control – that has potential applications for control of biochemical systems I had not appreciated before.
- Publications
    - Published: Diekman, Casey O., Peter J. Thomas, and Christopher G. Wilson. "Eupnea, tachypnea, and autoresuscitation in a closed-loop respiratory control model." *Journal of Neurophysiology* 118.4 (2017): 2194-2215.
    - Under review: Eckford, Andrew W., and Peter J. Thomas. "The Channel Capacity of Channelrhodopsin and Other Intensity-Driven Signal Transduction Receptors." *arXiv preprint arXiv:1804.04533* (2018).
    - Under review: Schmidt, Deena R., Roberto F. Galan, and Peter J. Thomas. "Stochastic Shielding and Edge Importance for Markov Chains with Timescale Separation."
    - Published: Youngmin Park, Kendrick M. Shaw, Hillel J. Chiel, Peter J. Thomas, "The Infinitesimal Phase Response Curves of Oscillators in Piecewise Smooth Dynamical Systems", in press, European Journal of Applied Mathematics (special issue on theory and applications of nonsmooth dynamical systems). ArXiv version: http://arxiv.org/abs/1603.03503 Published online: 02 April 2018. https://doi.org/10.1017/S0956792518000128
    - Casey O. Diekman, Peter J. Thomas, and Christopher G. Wilson, "Experimental Validation of a Closed-Loop Respiratory Control Model using Dynamic Clamp." 40th An- nual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC'18).

Kang-Ling Liao
Tamkang University
Discuss research project with Prof. Avner Friedman

Presentation in the Mathematics department titled: *Applications of mathematics in biology*

Publications

1. **Kang-Ling Liao**, Xue-Feng Bai, and Avner Friedman, 2018, Mathematical modeling of anti-PD-1 and IL-27 synergy in inhibiting tumor growth, in revision.
2. **Kang-Ling Liao** and Avner Friedman, 2018, Mathematical modeling and analysis of anti-PD-1 and anti-CTLA-4 synergy in cancer immunotherapy, in preparation.

Xiulan Lai
Renmin University of China
Institute for Mathematical Sciences

I visited MBI to do my postdoctoral research work under the support of the "post-doctoral international exchange program" by the China Postdoctoral Science Foundation.

During the visit to MBI, I attended several workshops and almost all of the visitor seminars and postdoc seminars at MBI. I also did several presentations at the seminars. The details are as follows.

Workshops attended:
Mar 06-10, 2017 "Modeling of tissue growth and form"
Mar 27-31, 2017 "Hybrid multi-scale modeling and validation"
Apr 24-28, 2017 "Women advancing mathematical biology: Understanding complex biological systems with mathematics"
Apr 23-27, 2018 "Multiscale dynamics of infections"

Presentations:
2018 Mar MBI PostDoc Seminar, MBI, "A stochastic model of axonal organelle accumulation induced by molecular motor reduction".
2017 May MBI Visitor Seminar, MBI, "Combination therapy of cancer with cancer vaccination and immune checkpoint inhibitors: a mathematical model".
2017 Jan MBI PostDoc Seminar, MBI, "Exosomal Mirs in lung cancer: a mathematical model".

During my visit to MBI, I mainly made collaborations with professor Avner Friedman and professor Chuan Xue working on modeling about cancer combination therapy and intracellular transport. The details are follows.

Research:
Most of my work has focused on developing predictive models with deterministic or stochastic partial differential equations, based closely on biological and biomedical problems. The overarching theme of my research is mathematical modeling about cancer, specifically the combination therapies of cancer and biomarkers of cancer. Another focus of my research is multiscale modeling about intracellular transport, mainly axonal intracellular transport and pollen tube intracellular transport, and related diseases. Those projects have applied either computational techniques or analytical approaches.

Publications:
[1] Xiulan Lai, Andrew Stiff, Robert Wesolowski, Carson III William E and Avner Friedman, Modeling combination therapy for breast cancer with BET and immune checkpoint inhibitors, PNAS, accepted.

[2] Avner Friedman and Xiulan Lai, Combination therapy for cancer with oncolytic virus and checkpoint inhibitor: A mathematical model, PLoS ONE 13(2): e0192449, 2018.
[3] Xiulan Lai and Avner Friedman, Combination therapy for melanoma with BRAF/MEK inhibitor and immune checkpoint inhibitor: A mathematical model, BMC Systems Biology 11(70), 2017.
[4] Xiulan Lai and Avner Friedman, Combination therapy of cancer with cancer vaccine and immune checkpoint inhibitors: A mathematical model. PLoS ONE 12(5): e0178479, 2017.
[5] Xiulan Lai and Avner Friedman, Exosomal microRNA concentrations in colorectal cancer: A mathematical model, Journal of Theoretical Biology 415: 70-83, 2017.
[6] Xiulan Lai and Avner Friedman, Exosomal miRs in lung cancer: a mathematical model, PLoS ONE 11(12): e0167706, 2016.

Submitted:
[1] Xiulan Lai and Avner Friedman, How to schedule VEGF and PD-1 inhibitors in combination cancer therapy?
[2] Xiulan Lai and Avner Friedman, Mathematical modeling of clinical trials in metastatic breast cancer with combination of VEGF inhibitor and chemotherapy drugs.
[3] Wanda Strychakski, Sarah Bryant, Baasansuren Jadamba, Erini Kilikian, Xiulan Lai, Leili Shahriyari, Rebecca Segal, Ning Wei, and Laura A. Miller, Fluid dynamics of nematocysts ring.

Keshlan Govinder
University of KwaZulu-Natal, South Africa
Collaboration with Tony Nance and Grzegorz Rempala. Discussed "Identifiability" with TN and "Stochastic Systems" with GR. The discussions on "Identifiabilty" will link into a project I am currently working on with a student in Durban, South Africa. We are looking into combining systems of first order ODEs into single ODEs so that a group theoretic analysis can be undertaken. Since we intend looking at biologically relevant systems, the concept of identifiability will be crucial in determining these systems. I also used OSU library resources to obtain relevant references in these areas as well as for a project in Tsetse flies.

-The discussions will ultimately lead to publications and conference presentations.

Boseung Choi
Korea University Sejong Campus, Sejong, South Korea
I have visited MBI during 13 Aug. 2018 ~ 17 Aug. 2018 as a short term visitor of MBI. From 2014, I visited MBI every summer semester. I think that the MBI is the best research institute for collaborating Statistics, Applied Mathematics, and Health sciences (including life sciences and Bio sciences). At the MBI, I have a lot of chances to contact researchers from the U.S as well as the other countries. The main objective of visiting the MBI is to organize existing researches and to start new research. The facilities of the institute are well equipped to perform individual research or collaborative research, and the staffs of the institute are well trained to support my studies and their services are very fast and friendly.

I've visited the MBI every summer semester from 2014 and two times in winter semester. Usually I spent a month but I stayed two weeks at this visiting. So I did not attend any workshop at time time. The MBI has only capstone design for under graduate students.

Statistical inferences for epidemic modeling - The SIR model is perhaps one of the most popular models in biosciences. However, it is hard to fit to individual-based data. We suggest an alternative approach based on the aggregation of the individual-based stochastic SIR. This leads to an interesting survival analysis interpretation of the classical deterministic SIR equation. Will illustrate with data from recent H1N1 epidemic.

Statistical modelling of the spread of Ebola virus – with Grezegorz Rempala (MBI director), Omar Saucedo (Postdoc of MBI), and Sydney Busch (REU attendee student). The random graphs can be served as models for social networks. In a random graph, individuals in a population are represented by vertices and transmission links between vertices are represented using edges. We applied the random graph method to disease spread modeling. The disease spreads can be modeled using random graph model along the social network obtained. In order to model the spread of Ebola virus in a small town in Republic of Congo, we utilized the random graph model. We also utilized Markov Chain Monte Carlo approach for the Bayesian estimation model.

Publications:
-Harmful Algal Blooms and non-alcoholic liver disease: focusing on the areas near the Four Major Rivers in South Korea. Submitted.
-Modeling household transmission dynamics: Application to Diarrheal disease in sub-Saharan Africa, Plos One, revised.
-Choi, B., Rempala, G., and Kim, J. K. (1017) Beyond Michaelis-Menten: accurate and efficient estimation of enzyme kinetic parameters, Scientific Reports. Open access journal.
-Schwartz, E., Choi, B., and Rempala, A. (2015). Estimating epidemic parameters: Application to H1N1 pandemic data, Mathematical Biosciences, 270, 198-203.

OHIO STATE UNIVERSITY COURSE RELEASE VISITORS

- Avner Friedman (Mathematics)
- Marty Golubitsky (Mathematics)
- Sebastian Kurtek (Statistics)
- Ayaz Hyder (College of Public Health)
- Yuan Lou (Mathematics)
- Matthew Pratola (Statistics)
- Joe Tien (Mathematics)

COURSE RELEASE REPORTS

Avner Friedman
Distinguished University Professor, Department of Mathematics
I have been working extensively with Xiulan Lai, who is a postdoc supported by China, who will be at the MBI for two years.

I also worked with visitors Nourridine Siewe, Yangjin Kim, Kang-Ling Liao and Wenrui Hao who came several times to the MBI during 2017.

The research papers that came out are

1. (with N. Siewe, A. Yakubu, A. Satoskar) *Granuloma formation in Leishmaniasis: A mathematical model*, J. Theoretical Biology, Vol. 412 (2017), 48-60.
2. (with X. Lai) *Exosomal microRNA concentrations in colorectal cancer*, J. Theor. Biol., Vol 416 (2017), 70-83.
3. (with W. Hao, S. Gong, S. Wu, J. Xu, and M. Go) *A mathematical model of aortic aneurysm formation*. PLoS ONE, (2017) DOI: 10.137.0170807, 22 pages.
4. (with W. Hao, H. M. Komar, P. A. Hart, D. Conwell, G. Lesinski) *A mathematical model of chronic pancreatitis*, PNAS, Vol. 114 (2017), 5011-5016.
5. (with X. Lai) *Combination therapy of cancer with cancer vaccine and immune check point inhibitors: A mathematical model*, PLoS ONE, (2017) DOI:10.1371.0178479, 24 pages.
6. (with X. Lai) *Combination therapy for melanoma with BRAF/MEK inhibitor and immune checkpoint inhibitor: A mathematical model*, BMC System Biology, (2017) 11:70 DOI:10.1186, 18 pages.
7. *Free Boundary Problems arising in biology*, Discrete and Continuous Dynamical Systems, Vol. 23 (2018), 193-202.
8. (with W. Hao) *The role of exosomes in pancreatic cancer*, Bull. Math. Biology, DOI 10.1007/11538-017-0254-9 (2017) 23 pages.
9. (with X. Lai) *Combination therapy of oncolytic virus and checkpoint inhibitor*, PLoS ONE, in revision.
10. (with N. Siewe) *Chronic hepatitis B virus and liver Fibrosis: A mathematical model*, PLoS One, submitted.
11. (with Y. Kim, Y. Yoo, and B. Kaur) *Complex Role of NK cells in regulation of OV-Bortezomib therapy*, PNAS in revision.
12. (with X. Lai, Aa. Stiff, R. Wesolwski, and W. Carson) *Combination therapy for breast cancer with BET inhibitor and immune checkpoint inhibitor: A mathematical model*, PNAS, submitted
13. (with K. L. Liao and X. F. Bai) *Mathematical modeling of anti-PD-1 and IL-27 Synergy in inhibiting tumor growth*, to be submitted to PLoS ONE.

Some of the papers were jointly with biomedical researchers at OSU, e.g. Greg Lesinski, Balveen Kaur, and Willilam Carson.

Nicola Moise from the medical school in Bucharest, Romania, came (with his own funding) for two weeks, and we are currently working on a project in Rheumatoid Arthritis.

Martin Golubitsky
Distinguished University Professor, Department of Mathematics
Purpose of Visit to MBI and nature of work: Participate in the Emphasis Program on *Control in Biology and Medicine*, organize the *MBI Online Colloquium Series*, and continue my research program.

1. I participated in and gave an invited talk in Workshop 4 on *Sensori-Motor Control of Animals and Robots* (my talk was titled *Properties of Network Solutions*).
2. I participated in and gave a talk in the *MBI Visitors Seminar* (my talk was titled *Homeostasis and Singularities*)
3. I attended a number of talks in the other three workshops
4. I moderated the four MBI online Colloquia.

Research

I submitted two papers on research partially carried out at MBI (see below) and made substantial progress on a project on bifurcations in fully inhomogeneous networks. This research is in cooperation with Claire Postletwaite (MBI longterm visitor), Punit Ghandi and Yangyang Wang (MBI Postdoctoral Fellows), and Ian Stewart. I also continued work on two projects (binocular rivalry and infinitesimal homeostasis) and have papers in preparation (see below).

Publications

1. M. Golubitsky and I. Stewart. Homeostasis with multiple inputs. *SIAM J. Appl. Dynam. Sys*. Submitted.
2. F. Antoneli, M. Golubitsky, and I. Stewart. Homeostasis in a feed forward loop gene regulatory motif. *J. Theoret. Biol*. Submitted.
3. M. Golubitsky, Z-L Lin, and Y. Zhao. Predicting patterns of interocular grouping from the symmetry of rivalry network models. In preparation.
4. W. Duncan, J. Best, M. Golubitsky, H.F. Nijhout, and M. Reed. Homeostasis despite instability. In preparation.

Sebastian Kurtek
Assistant Professor, Department of Statistics

I am visiting the MBI during the Fall 2017 emphasis program on Control in Biology and Medicine. I was mainly interested in learning more about this topic and how it may be related to shape analysis, and more broadly, analysis of geometric data structures. I was also interested in interacting with the MBI postdoctoral fellows and other visitors.

I was able to spend most of my Thursdays during the Fall semester in the office provided to me by the MBI (I had teaching obligations on Mondays, Wednesdays and Friday as well as other meetings with students and colleagues on Tuesdays).

I attended the following postdoctoral fellow seminar presentations:

1. *Gender differences in hepatic one-carbon metabolism* by Farrah Sadre-Marandi
2. *Spatial Dynamics of Vector-Borne Diseases* by Omar Saucedo
3. *Mechanics of nuclear pore transport* by Ben Fogelson
4. *Piecewise smooth models of a biological motor control system* by Yangyang Wang
5. *A Bundled Solution for High-Dimensional Informatics Problems* by Reginald McGee

I gave a seminar titled *Statistical Shape Analysis of Surfaces Using Square Root Normal Fields*.

One postdoctoral fellow, Colin Klaus, was especially interested in the topics I presented. I sent him some relevant materials that he requested and plan to follow-up early next semester. At the beginning of the semester, I became involved in a research project spearheaded by postdoctoral fellow Punit Gandhi. He is interested in studying vegetation patterns. We met twice over the course of the semester, once with Prof. Kate Calder and the second time with Prof. Calder and Punit's collaborators from the University of Chicago (Justin Finkel who is a graduate student and

Prof. Mary Silber). In particular, they were interested in using shape analysis of curves to cluster the vegetation patterns. After our meeting, I sent Justin an implementation of the methods we discussed and have since followed-up with him on his progress. Most recently, I attended the postdoctoral fellow presentation by Reginald McGee and have identified some research directions related to his work. I am hoping to follow-up with Reginald before the end of the semester to discuss these ideas. Finally, while I did not attend any of the four workshop in their entirety, I was able to attend several talks across the entire semester (mostly on Thursday of the workshop).

• Research: shape analysis of vegetation pattern curves
• Publications: there is a potential for a publication if results of the above research are promising

Joseph Tien
Mathematics
Purpose of Visit to MBI and nature of work
The 2018 emphasis semester was on Infectious Diseases: Data, Modeling, Decisions. I was on the steering committee for this emphasis semester, and was also one of the organizers for the third workshop on Disease Ecology. MBI provided course release to support my participation in these worshops.

I attended the four workshops in spring 2018: Host-Pathogen Dynamics (February 19-23); Socioepidemiology (March 5-9); Disease Ecology / Eco-epidemiology (March 26-30); Multiscale dynamics of infections (April 23-27). I helped organize the Disease Ecology workshop.

I also attended some of the Visitor Seminars, and gave a Visitor Seminar on April 17 (From infectious disease to Twitter, Nazis, and Trump: encounters with contagion of a different kind).

On the research side I continued mentoring Omar Saucedo (MBI postdoc) on a project studying vector-host disease dynamics on discrete spatial networks. This project has come together nicely in the past semester and we expect to submit a manuscript on this soon.

Matthew Osborne (PhD student, OSU mathematics) was invited to give a talk on his research at the U. Illinois (Mathematical Biology seminar) as a result of the MBI emphasis semester. This has resulted in a potential collaboration with Dolores Albarracin at U. Illinois.

Yuan Lou
Department of Mathematics
Purpose of Visit to MBI and nature of work: I have been working on the mathematical modeling of disease dynamics since 2007. I have published three papers with Linda Allen et al. (SIAP 2007, DCDS-A 2008, JMB 2009) and more recently two more articles (JDE 2016, 2017) on spatial disease spreading. The semester program of **Infectious Diseases: Data, Modeling, Decisions** at MBI is very close to my research interest and I learned a great deal from participating these workshops.

-I attended 4 workshops in the semester program of **Infectious Diseases: Data, Modeling, Decisions.** I interacted with the workshop organizers and participants, e.g., Pauline van den Driessche, Mark Lewis, Linda Allen.

-I gave one seminar presentation on “Finding ESS for Evolution of Movement” at the MBI visitor’s seminar on Jan 30, 2018. I also attended this seminar series.

-I gave a talk at the workshop “Disease Ecology and Eco-epidemiology”, with the title “Spatial SIS Models in Heterogeneous Environments”.

Any products that were or will be a result of your stay in MBI (please list anything you find applicable here)
-Research: I am currently preparing a manuscript on the disease spreading and MBI support will be acknowledged.

- I also attended IDI EEPH meeting, organized by Joe Tien and Jiyoung Kim. Date: May 9, 2018

Matthew Pratola
Statistics
My motivation for visiting the MBI during Spring 2018 was to foster opportunities for potential collaborations on applied projects that combine mathematical models with data with the goal of inferring mechanisms at work in biosciences applications. The Spring 2018 MBI program, *Infectious Disease: Data, Modeling and Decisions*, appeared to be a good opportunity to find such collaborations given my statistical research in computer experiments and nonparametric regression modeling. As it turns out, visiting the MBI was an excellent experience as I have found that this goal was achieved during my stay.

While at the MBI, I attended the first three workshops – Host-Pathogen Dynamics, Socioepidemiology and Disease Ecology – and would have happily attended the fourth workshop on Multiscale Dynamics of Infection were it not for a scheduling conflict. I attended numerous guest lectures and postdoc seminars, and regularly joined the MBI postdocs for lunch to further opportunities for interaction. I also gave a research seminar on Bayesian Statistical Uncertainty Quantification on January 23rd, 2018, which provided an overview of my areas of research that I believed would be most relevant to the MBI audience.

During my visit, my most productive research discussions have been with Dr. Daniel Linder (Department of Biostatistics and Epidemiology, Augusta University) who was also a 2018 spring semester visitor. His research in gene regulation and reaction networks involves complex stochastic models with likelihoods that are numerically expensive to evaluate and often have no closed-form expression. This makes Bayesian inference for such models extremely challenging. This problem dovetails nicely with my most recent work in computer experiments where I devised an approach to statistically calibrate stochastic simulators – simply speaking, this is a method to perform approximate inference for computationally constrained stochastic models.

Dr. Linder has previously attempted exact inference for one such model, which took about 1 month of computing time and involved ~500,000 realizations from the stochastic simulator. As such, a more efficient means of model fitting would be very beneficial in terms of exploring various modeling alternatives, sensitivities, etc. Applying my methodology to this problem involved 10,000 realizations simulated over ~2 days, and 1 hour to perform statistical calibration on the resulting dataset. Figure 1 summarizes the calibrated predictions of this procedure (black lines) to

the observations (red dots) for a test dataset. Clearly, this successful initial exploration suggests Dr. Linder and I can make large improvements to inference for such complex models by combining ideas from our respective areas of research.

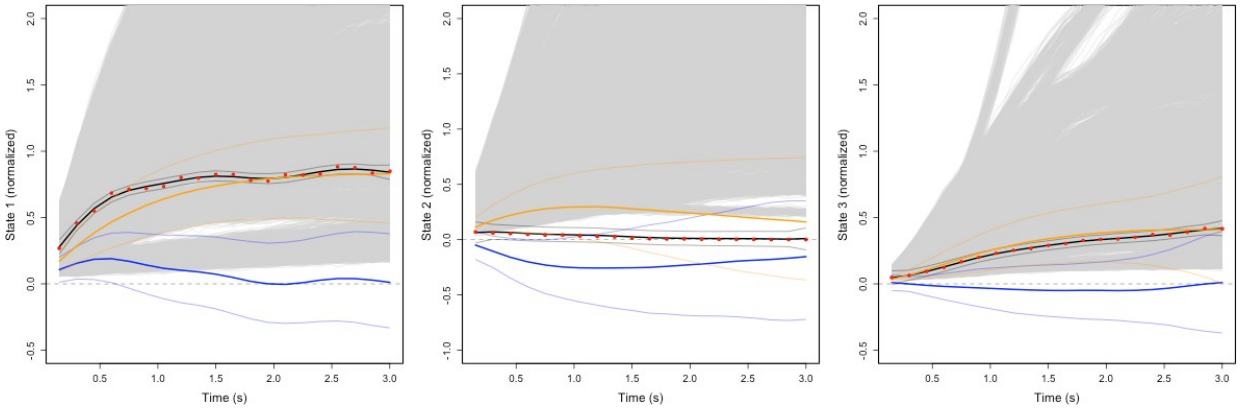


Figure 1: Prior runs of the stochastic simulator using a 100-run LHS sample with 100 realizations each (grey) for 3 states. Simulated observations are shown in red while the calibrated predictions are shown as the solid black line (light black lines represent 95% uncertainty interval). Solid orange line represents the emulated calibrated simulator model (light orange lines represent 95% uncertainty interval). Solid blue line represents additive model discrepancy (light blue lines represent 95% uncertainty interval).

Based on these promising initial results, Dr. Linder and I have been continuing our research discussions since the end of Spring semester. We plan to submit a research grant this fall to explore 3 key problems we have identified during our discussions, and at minimum foresee publishing one paper even if this grant were not funded.

Given my very positive and productive experience during the Spring 2018 MBI visitorship, I have requested (and been granted) the opportunity to retain office space at the MBI and continue spending time there in the future, starting during the Fall 2018 semester. I plan to spend ~1 day per week at the MBI this fall to enable further opportunities for research collaborations to occur.

Thank-you again for the wonderful opportunity to take part in the MBI during Spring 2018 as part of the MBI visitorship program!

VISITOR SEMINAR

With the number and scientific breadth of visitors (of all varieties) seen above, MBI added a seminar series featuring talks by MBI Visitors.

The 2017-2018 MBI Long Term Visitor Seminar speakers were:

1. September 8, 2017, **Martin Wechselberger** (University of Sydney)
   Two-stroke relaxation oscillators
   https://mbi.osu.edu/event/?id=1174

2. September 19, 2017, **David Murrugarra** (University of Kentucky)

A Near-Optimal Control for Stochastic Gene Regulatory Networks
https://mbi.osu.edu/event/?id=1175

3. September 26, 2017, **Claire Postlethwaite** (University of Auckland)
   Spirals and heteroclinic cycles in Rock-Paper-Scissors
   https://mbi.osu.edu/event/?id=1176

4. October 10, 2017, **Graham Donovan** (University of Auckland)
   Clustered ventilation defects in asthma
   https://mbi.osu.edu/event/?id=1177

5. October 17, 2017, **Marty Golubitsky** (Ohio State University)
   Homeostasis and Singularities
   https://mbi.osu.edu/event/?id=1178

6. October 27, 2017, **Léo Girardin** (Université Pierre et Marie Curie)
   Non-cooperative Fisher KPP systems: traveling waves and long-time behavior
   https://mbi.osu.edu/event/?id=1179

7. November 7, 2017, **Sebastian Kurtek** (The Ohio State University)
   Statistical Shape Analysis of Surfaces Using Square Root Normal Fields
   https://mbi.osu.edu/event/?id=1194

8. December 12, 2017, **Maciej Pietrzak** (The Ohio State University)
   Characterization of Cellular Immunome and T-cell Receptor Repertoires in Leukemia Samples
   https://mbi.osu.edu/event/?id=1195

9. January 16, 2018, **Leili Shahriyari** (Ohio State University)
   Computational models for tumorigenesis to obtain effective cancer treatments
   https://mbi.osu.edu/event/?id=1198

10. January 23, 2018, **Matthew Pratola** (Ohio State University)
    Bayesian Statistical Uncertainty Quantification: Inference and Prediction with Computational Models and Big Data
    https://mbi.osu.edu/event/?id=1199

11. January 30, 2018, **Yuan Lou** (The Ohio State University)
    Finding ESS for Evolution of Movement
    https://mbi.osu.edu/event/?id=1200

12. February 6, 2018, **Calistus Ngonghala** (University of Florida)
    Rural poverty: a dynamical and ecological perspective
    https://mbi.osu.edu/event/?id=1201

13. February 13, 2018, **Pamela Pyzza** (Ohio Wesleyan University)
    Idealized Models of Insect Olfaction

https://mbi.osu.edu/event/?id=1202

14. February 27, 2018, **Fernando Antonelli** (Universidade Federal De Sao Paulo)
    Homeostasis, Singularities and Gene Regulatory Networks
    https://mbi.osu.edu/event/?id=1203

15. April 3, 2018, **Daniel Linder** (Augusta University)
    Parameter Inference in Stochastic Reaction Networks
    https://mbi.osu.edu/event/?id=1205

16. April 10, 2018, **Megan Powell** (University of St. Francis)
    Tasmanian devils and devil facial tumor disease
    https://mbi.osu.edu/event/?id=1206

17. April 12, 2018, **Ayaz Hyder** (The Ohio State University)
    A theoretical model for racial health disparities in an urban US city: Linking theory and concepts from economics, health and sociology
    https://mbi.osu.edu/event/?id=1223

18. April 17, 2018, **Joe Tien** (The Ohio State University)
    From infectious disease to Twitter, Nazis, and Trump: encounters with contagion of a different kind
    https://mbi.osu.edu/event/?id=1207

19. April 19, 2018, **Kevin Passino** (The Ohio State University)
    Mathematics, Technology, and Mental Illness
    https://mbi.osu.edu/event/?id=1222

NATIONAL COLLOQUIUM

Thousands of scientists working at the interface of the mathematical and biological sciences have participated in programs at the Mathematical Bioscience Institute (MBI), where they have found out about the latest advances in their fields. MBI is expanding its program with the online MBI National Mathematical Biology Colloquium. This series will be available as an online interactive event and as on-demand streaming. The colloquia will cover the many fields of mathematical biology. The goal of this program is twofold: to enable large numbers of researchers to hear about recent advances in the field, and to connect the mathematical biology community worldwide.
The online MBI National Colloquium will give individuals and groups the opportunity to watch talks and to ask questions of the speaker. You can interact with leading researchers and key opinion leaders from your classroom to the comfort of your own office. You can be an active part of discussions taking place in emerging areas of mathematical biology. If you are unable to make a talk, you can view it on-demand at a later date.

The 2017-2018 MBI Colloquium speakers were:

1. September 20, 2017, **James Collins** (Massachusetts Institute of Technology)
   Synthetic Biology: Life Redesigned
   https://mbi.osu.edu/event/?id=1147

2. October 18, 2017, **John Tyson** (Virginia Polytechnic Institute and State University)
   Network Dynamics and Cell Physiology
   https://mbi.osu.edu/event/?id=1153

3. November 8, 2017, **Kristin Swanson** ()
   Every Patient Deserves Their Own Equation: Patient-Specific Mathematical NeuroOncology
   https://mbi.osu.edu/event/?id=1149

4. December 6, 2017, **Lisa Fauci** (Tulane University)
   Biological Fluid Dynamics at the Microscale: Nonlinearities in a Linear World
   https://mbi.osu.edu/event/?id=1150

5. January 17, 2018, **Alan Perelson** (Los Alamos National Laboratory)
   Modeling Antibodies and HIV Cure
   https://mbi.osu.edu/event/?id=1155

6. February 14, 2018, **Alan Hastings** (University of California)
   Dynamics and control of spatial ecological populations
   https://mbi.osu.edu/event/?id=1156

7. March 21, 2018, **Philip Maini** (University of Oxford)
   Modelling Collective Cell Motion in Biology
   https://mbi.osu.edu/event/?id=1157

8. April 18, 2018, **Marc Suchard** (University of California)
   High-dimensional Phenotypes on Evolutionary Trees: Efficient Algorithms and New Models
   https://mbi.osu.edu/event/?id=1158

PRODUCTS

Publications

2017-18 Publications which acknowledge "Mathematical Biosciences Institute" (according to Google Scholar in mid July 2017):

Park, J., & Lin, S. (2017). A random effect model for reconstruction of spatial chromatin structure. *Biometrics*, *73*(1), 52-62.

Park, J., & Lin, S. (2017). A random effect model for reconstruction of spatial chromatin structure. *Biometrics*, *73*(1), 52-62.

Lai, X., & Friedman, A. (2017). Combination therapy of cancer with cancer vaccine and immune checkpoint inhibitors: A mathematical model. *PloS one*, *12*(5), e0178479.

Viglialoro, G., & Woolley, T. E. (2017). Eventual smoothness and asymptotic behaviour of solutions to a chemotaxis system perturbed by a logistic growth. *Discrete & Continuous Dynamical Systems-B*, 453-474.

Amrein, M., & Wihler, T. P. (2017). Adaptive pseudo-transient-continuation-Galerkin methods for semilinear elliptic partial differential equations. *Numerical methods for partial differential equations*, *33*(6), 2005-2022.

Pradenas, B., Araya, I., Clerc, M. G., Falcón, C., Gandhi, P., & Knobloch, E. (2017). Slanted snaking of localized Faraday waves. *Physical Review Fluids*, *2*(6), 064401.

Altenberg, L. (2017). Probing the axioms of evolutionary algorithm design: Commentary on "On the mapping of genotype to phenotype in evolutionary algorithms" by Peter A. Whigham, Grant Dick, and James Maclaurin. *Genetic Programming and Evolvable Machines*, *18*(3), 363-367.

Anderson, A. R., & Maini, P. K. (2018). Mathematical Oncology. *Bulletin of mathematical biology*, *80*(5), 945-953.

Bates, D. J., Newell, A. J., & Niemerg, M. E. (2017). Decoupling highly structured polynomial systems. *Journal of Symbolic Computation*, *79*, 508-515

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Schwartzbaum, J., Wang, M., Root, E., Pietrzak, M., Rempala, G. A., Huang, R. P., ... & Grimsrud, T. K. (2017). A nested case-control study of 277 prediagnostic serum cytokines and glioma. *PloS one*, *12*(6), e0178705.

Friedman, A., & Lai, X. (2018). Combination therapy for cancer with oncolytic virus and checkpoint inhibitor: A mathematical model. *PloS one*, *13*(2), e0192449.
Pietro-Luciano Buono, Martin Krupa & Ian Stewart (2017) Special issue for Martin Golubitsky, *Dynamical Systems*, 32:1, 1-3, DOI: 10.1080/14689367.2017.1280905

Sadre-Marandi, F., & Das, P. Extension of Caspar-Klug theory to higher order pentagonal polyhedra. *Computational and Mathematical Biophysics*, *6*(1), 1-13.

Shahriyari, L. (2017). Effect of normalization methods on the performance of supervised learning algorithms applied to HTSeq-FPKM-UQ data sets: 7SK RNA expression as a predictor of survival in patients with colon adenocarcinoma. *Briefings in bioinformatics*.

Bollas, A., & Shahriyari, L. (2017). The role of backward cell migration in two-hit mutants' production in the stem cell niche. *PloS one*, *12*(9), e0184651.

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Allen, L. J., Jang, S. R., & Roeger, L. I. (2017). Predicting population extinction or disease outbreaks with stochastic models. *Letters in Biomathematics*, *4*(1), 1-22.

Schmidt, M. H., Swang, T. W., Hamilton, I. M., & Best, J. A. (2017). State-dependent metabolic partitioning and energy conservation: A theoretical framework for understanding the function of sleep. *PloS one*, *12*(10), e0185746.

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Kaufmann, D., Theriot, J. J., Zyuzin, J., Service, C. A., Chang, J. C., Tang, Y. T., ... & Brennan, K. C. (2017). Heterogeneous incidence and propagation of spreading depolarizations. *Journal of Cerebral Blood Flow & Metabolism*, *37*(5), 1748-1762.

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Vakulenko, S. A., Sudakov, I., & Mander, L. (2018). The influence of environmental forcing on biodiversity and extinction in a resource competition model. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, *28*(3), 031101.

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Xue, C., & Jameson, G. (2017). Recent Mathematical Models of Axonal Transport. In *Stochastic Processes, Multiscale Modeling, and Numerical Methods for Computational Cellular Biology* (pp. 265-285). Springer, Cham.

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INSTITUTE PARTNERS IN 2017-2018

The MBI Institute Partner (IP) program promotes the involvement of the international math biosciences community in MBI programs. Institute Partners receive direct benefits and opportunities enabling them to support, guide and participate in MBI research and education programs.

Institute Partners:

1. Battelle Memorial Institute
2. Boston University
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13. Iowa State University
14. Konkuk University
15. Korea University - Sejong Campus
16. McGill University
17. Michigan State University
18. Mississippi State University
19. Moffitt Cancer Center
20. Mount Sinai School of Medicine
21. National Autonomous University of Mexico (UNAM)
22. National Tsing Hua University
23. New Jersey Institute of Technology
24. Ohio University
25. Pennsylvania State University

26. Princeton University
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59. University of Utah
60. University of Washington
61. University of Waterloo
62. University of Wisconsin-Milwaukee
63. University of Wyoming
64. Vanderbilt University
65. Virginia Commonwealth University
66. Virginia Polytechnic Institute and State University

PUBLIC LECTURE SERIES

MBI continued to be instrumental in the Science Sundays Public Lecture Series at OSU, including sponsoring a lecture by **Matt Kahle**. Science Sundays lectures are held monthly during the academic year, usually attract 150-250 individuals, and provide a forum to interest, engage, and

inform the public about a wide range of current and emerging issues in science that touch our everyday lives. http://artsandsciences.osu.edu/science-sundays

1. September 10, 2017, **Frederic Bertley**, PhD, President and CEO, Center of Science and Industry (COSI)
   Paying Attention to the Importance of the Scientific Revolution Amid Cluelessness
   https://www.youtube.com/watch?v=vAYpcm-vyqQ

2. October 15, 2017, **Jonathan Yewdell**, (MD, PhD, Chief, Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases)
   A Practical Guide to Becoming a Priest of Scientific Methodism
   https://www.youtube.com/watch?v=_JR3Bnyb-Eg

3. November 12, 2017, **Ruchika Prakash** (Associate Professor, Psychology, Ohio State)
   Mindfulness for the Aging Brain
   No video link available

4. December 3, 2017, **Joe Lykken**, (Theoretical Physicist, Deputy Director and Chief Research Officer of Fermilab)
   Particle Physics: New Research Frontiers
   https://www.youtube.com/watch?v=nl-OAA3wvVM

5. January 21, 2018, **Rebecca Reczek** (Associate Professor, Marketing, Ohio State)
   Do Healthy Diets Make Empty Wallets? How Consumer Beliefs Shape Food Choice
   https://www.youtube.com/watch?v=qkUG9pLP-Bw&feature=youtu.be

6. February 18, 2018, **Matt Kahle** (Associate Professor, Mathematics, Ohio State)
   Archimedes: Mathematical Superhero of the Ancient World
   https://youtu.be/n7DN5Mvp7nc

7. March 18, 2018, **Amanda Petford-Long** (Distinguished Fellow, Materials Science Division, Argonne National Laboratory; Northwestern University Professor of Materials Science and Engineering)
   How Microscopy Can Help Understand Nanomaterials
   No video link available

8. April 15, 2018, **Alberto Cairo** (Knight Chair in Visual Journalism, University of Miami)
   Visual Trumpery
   No video link available

DIVERSITY INITIATIVES

MBI Team Attending Diversity Conference at Other Institutions

Adriana Dawes – Associate Director to MBI
Modern Math Workshop (at SACNAS)
Oct. 18-19, 2017

Salt Lake City, UT
https://icerm.brown.edu/mmw2017/

Adriana Dawes – Associate Director to MBI
NSF INCLUDES Summit: Broadening Participation through Center-Scale Research
Jan. 8-10, 2018
Alexandria, VA
http://www.mtnsfepscor.org/index.php/news/events/nsf-includes-summit-broadening-participation-through-center-scale-research

Omar Saucedo - MBI Postdoctoral Fellow
2017 Field of Dreams Conference
Nov 2 - 5, 2017
St. Louis, MO
https://mathalliance.org/2017-field-of-dreams-conference/
https://mathalliance.org/2017-field-of-dreams-conference-review/
https://mathalliance.org/wp-content/uploads/2017/11/201-Agenda.pdf

COMMUNITY INVOLVEMENT IN MBI PROGRAMS

Third Workshop on Omics Data Analysis
September 5 -7, 2017
3-day workshop organized by BSD faculty and staff that included instructors from BSD, Statistics Department, Biostatistics (College of Public Health), Mathematical Biology Institute, Bioinformatics (Biomedical Informatics Department). Open to all postdoctoral individuals and junior faculty at OSU who wish to train and gain expertise in genomics data analyses: about 40 postdocs and junior faculty from different OSU labs/groups attended.

Speakers: Guy Brock (BMI), Kevin Coombes (BMI), Soledad Fernandez (BMI), Shili Lin (Statistics), Joseph McElroy (BMI), Maciej Pietrzak (BMI), Grzegorz Rempala (CPH/MBI), Xiaokui Mo, (BMI), Lianbo Yo (BMI)

OSU Data Analytics Month
October 2017
OSU celebrated a month devoted to Data Analytics, and several institutes and centers participated through hosting various events. MBI contributed seven seminar talks and hosted a workshop on viromics (see next item).

Viromics Workshop at The Ohio State University
October 18-20, 2017

Organizers: Matthew B. Sullivan (OSU), Mya Breitbart, Bonnie Hurwitz, David Páez-Espino (JGI), Simon Roux (JGI), Arvind Varsani (ASU), and Steven Wilhelm

Speakers: Ben Bolduc (OSU), Simon Roux (JGI), David Paez-Espino (JGI), and Arvind Varsani (ASU).

On Oct 18-20, 2017, 52 researchers from around the world converged on the MBI to train in how to use sequence datasets to understand viruses of microbes in complex communities. Microbes are now recognized as integral to ecosystem function in the oceans, soils, bioreactors, and humans, but recent evidence suggests microbial roles are strongly influenced by viruses. Sequence-based, viral metagenomic (viromic) approaches have transformed the study of viruses in these complex communities by having augmented known viruses 100-fold, revealing how viruses directly manipulate core microbial metabolisms (e.g. photosynthesis and C, N and S cycling), and providing ecological perspectives on their distributions and drivers throughout the global oceans. However, developing methodological and informatics standards, as well as interactions with mathematicians to maximize best practices and utilization of the large-scale datasets all represent critical bottlenecks to the field.

This 2.5-day viromics workshop kicked off with a mini-symposium to showcase diverse virome-enabled science and then sought to introduce graduate students and postdocs to the informatics tools (iVirus and IMG/VR) available to develop biological understanding of viruses from viral and microbial metagenomic datasets. Open discussions of best practices were held throughout and the 52 participants (including teachers) from 9 countries attended, including representation from 7 Ohio State labs, contributed greatly to helping the field advance. The workshop was partially supported by the MBI, Gordon and Betty Moore Foundation, and OSU College of Arts and Sciences.

TRIPODS Center Summer School

May 14-18, 2018

The summer school, primarily aimed at early career researchers, covered some basics as well as recent developments on several important topics in Topology, Geometry and Data Analysis. In particular, the topics included recent developments in persistent homology, topological algorithms, and statistics on manifolds and shape spaces.

TRIPODS Center Workshop

May 21-25, 2018

Topological and geometric ideas have already shown promises in producing novel perspectives and powerful algorithms for analyzing complex and diverse data. As the theory and foundations of topological data analysis continue to mature, we are presented with great opportunities to consolidate existing synergy as well as to establish new connections and collaborations among computational scientists, mathematicians, and statisticians, so as to form new perspectives and develop novel methodologies / algorithms for modern data analysis. This workshop presents a timely platform to help achieve these goals.

Conference Board of Mathematical Sciences (CBMS) Conference – Elastic Functional and Shape Data Analysis (EFSDA)

July 16-20, 2018

Topic Area

This Conference Board of the Mathematical Sciences (CBMS) conference will feature an intensive lecture series on elastic methods for statistical analysis of functional and shape data, using tools from Riemannian geometry, Hilbert space methods, and computational science. The main focus of this conference is on geometric approaches, especially on using elastic Riemannian metrics with desired invariance properties, and square-root representations that simplify computations. These

approaches allow joint registration and statistical analysis of functional data, and are termed elastic for that reason. The statistical goals include comparisons, summarization, clustering, modeling, and testing of functional and shape data objects.

Primary Lecturer
Prof. Anuj Srivastava is a Professor of Statistics and a Distinguished Research Professor at Florida State University (FSU) in Tallahassee, FL. His main expertise lies in the use of techniques from algebra and differential geometry in deriving statistical inferences on nonlinear manifolds. Specifically, along with his colleagues, he has developed comprehensive Riemannian frameworks for shape analysis of objects, including scalar functions, Euclidean curves, 2D surfaces, and neuronal trees. He is an author, along with Prof. Eric Klassen of FSU, of a recently published Springer textbook on Functional and Shape Data Analysis. He has also published more than 200 papers in refereed journals and proceedings of refereed international conferences. He is a fellow of the IEEE, IAPR, and ASA.

Additional Lecturers
- Prof. Eric Klassen, Department of Mathematics, Florida State University
- Prof. Veera Baladandayuthapani, Department of Biostatistics, University of Texas MD Anderson Cancer Center
- Prof. Laurent Younes, Department of Applied Mathematics and Statistics, Johns Hopkins University
- Prof. Zhengwu Zhang, Department of Biostatistics and Computational Biology, University of Rochester

We gratefully acknowledge funding and support from the National Science Foundation CBMS grant, the Mathematics Research Institute, the Mathematical Biosciences Institute, the Department of Statistics at Ohio State, and the NSF TRIPODS grant.

Co-sponsored postdocs and visitors that were partially supported by MBI
• **Reginald McGee** – Postdoctoral Fellow
• **Inom Mirzaev** – Postdoctoral Fellow
• **Amir Taheri** – Postdoctoral Fellow
• **Maciej Pietrzak** – Long Term Visitor
• **Ben Fogelson –** Postdoctoral Researcher
• **Xiulan Lai** – Long Term Visitor

EXTERNAL EVALUATION OF MBI

MBI has a contract with Strategic Research Group (https://strategicresearchgroup.com/) to perform an independent evaluation of select MBI programming based on online questionnaires and personal interviews. Reports from the REU and Woman Advancing Mathematical Biology (WAMB) are attached in the "Accomplishments" section of the research.gov online reporting form.

PROGRAM INITIATIVES FOR NEXT YEAR

2018-2019 Programs – No Cost Extension Year

Current Topic Workshop (CTW): Collective Behavior and Phenomena in Biology, Sept 10-12, 2018

Organizers: Simon Garnier (Department of Biological Sciences, NJIT), Jason Graham (Mathematics, University of Scranton)

This CTW is a collaborative workshop for researchers and students with research interests in collective behavior and emergent phenomena in biology and its applications. The participants will be organized into interdisciplinary teams according to their interests and complementary skills. Each team will be tasked with exploring, analyzing and modeling original data sets provided by biologist attendees. The event will be similar in spirit to a hackathon in computer science, with the goal of finding new ways to understand the provided biological data. We emphasize that the workshop is meant to involve active participation with attendees working together across disciplines to solve problems in current research. In addition, regular debriefing sessions will be organized throughout the days of the workshop in order for each team to provide updates to and receive feedback from the rest of the participants on their progress.

LIST OF PROJECTS

#	Leaders	Co-leaders	Titles
1	Helen McCreery	Allison Shaw	Exploring group strategy and cohesion during obstacle navigation
2	Ted Pavlic	Tomer Czaczkes	Collectives and tradeoffs: Self-organized decision-making with multiple competing objectives
3	Albert Kao	James Crall	Choosing between rigid and flexible behavioral strategies: thermoregulation in the bumblebee Bombus impatiens as a case study
4	James Curley	Lisa O'Bryan	Modeling conflict strategies in social hierarchies
5	Erol Akcay	TBD	Dynamic feedbacks between social structure and behaviors
6	Simon Garnier	Jason M Graham	Models of multi-constraint optimization in self-organized systems

Emphasis Semester: Analyzing Macro and Micro Population Models

Workshop 1: Family-Based Genomic Studies, Sep 17-19, 2018

Organizers: Shili Lin (Statistics, The Ohio State University), Lara Sucheston-Campbell (Pharmacy Practice and Science, The Ohio State University), Asuman Turkmen (Department of Statistics, The Ohio State University)

The field of Genetic Epidemiology has historically focused on the inheritance of genetic factors and phenotypes within families. However, the increase in ever improving technologies brought a shift from familial study designs to genome wide association studies (GWAS) utilizing samples of unrelated individuals. While GWAS has yielded greater knowledge of genomic structure and disease associated variants, the estimated effect sizes are small and often to not explain a large proportion of disease heritability. One of the explanations for the missing heritability is that the variants identified in GWAS are common (> 5%) and thus we are missing an entire class of variation (rare) that substantially contributes to disease risk. The innovation of next-generation sequencing technology made the comprehensive discovery of rare variants feasible, however the sample size of unrelated individuals needed to identify associations between these rare variants and diseases is in the thousands (> 10,000 samples are necessary to detect a variant showing evidence of modest association with minor allele frequency 0.1%). While sequencing costs have decreased, the financial burden is still nontrivial and sample heterogeneity can easily confound results. Thus, efficient study designs and improved statistical approaches are necessary to untangle the contribution of rare variation to complex disease. Family studies have always been robust to confounding and a powerful approach for identifying genetic variation. In the age of sequencing, family studies are again an appealing approach for studying the relationship between complex disease and genetic variation.

This workshop will focus on the use of family studies in the hunt for disease associated genes, include the development of novel methodologies and statistics for assessing variant disease relationships as well as the important role of the family study design in a clinical sequencing setting.

Workshop 2: Math and the Microbiome, Oct 10-12, 2018

Organizers: Adriana Dawes (Dept of Mathematics/Dept of Molecular Genetics, The Ohio State University), Vanessa Hale (Dept of Veterinary Preventive Medicine, The Ohio State University), Matthew Sullivan (Department of Microbiology, The Ohio State University)

From the bacteria in our guts, to microbes involved in biodegradation and crop growth, to viruses in the ocean, some of Earth's tiniest organisms play some of the most important roles in global health, food production, and climate change. Advances in metagenomic sequencing technology including 16S, viromics, and mycobiomics - along with metabolomics, transcriptomics, and proteomics allow us to characterize these complex microbial communities and begin to understand their functions. This Big Data creates opportunities for data driven discovery and new data analytics, but Big Data also comes with challenges: Meaningful integration of multi-omic data has become increasingly critical to microbiome studies as recent work highlights the importance of community dynamics, interactions, and microbial ecology over the roles of individual microbes. For example, microbial metabolisms are now recognized to often be 'distributed' across consortia; viruses manipulate microbial metabolisms and population dynamics, and co-occurring fungi in most ecosystems are virtually unstudied but likely play key roles as well. Data integration techniques range from correlations to network analyses to genome-scale microbial community metabolic models that assess metabolite flux to ecosystem models that provide predictive power of which organisms drive key features of the system. Some of these techniques, like correlations, accommodate many types of –omic data but cannot account for the complex biology or ecology of a system. Other techniques, like metabolic modeling, better account for this complexity, but do not

yet integrate phenotypic –omic data (i.e. metabolomics, proteomics) well. Each of these techniques has advantages and limitations and new computational tools for data integration and modeling have rapidly developed over the last 2 years. Besides data integration, Whether studying environmental, gut, or industrial microbes, the ability to accurately identify and predict the structure and function of microbial communities has far-reaching potential and paves the way for microbial engineering in bioremediation, probiotic development, and sustainable agriculture.

In this 3-day workshop, we will take a genome to phonome approach with broad perspectives provided by mathematicians, biologists, and statisticians. We will also develop interdisciplinary working subgroups to consider the questions, challenges, tools, and needs of data integration and modeling in microbiome studies. Each participant will present a short talk (5 minutes, 3 slides) highlighting his or her research, perspectives, and challenges. The goal is to help develop a broadly collaborative community of math-enabled microbiome scientists with common research goals.

Workshop 3: Modeling and Analysis of Social Networks, Nov 7-9, 2018

Organizers: Ian Hamilton (Dept of Evolution, Ecology and Organismal Biology/Dept. of Mathematics, The Ohio State University), Keith Warren (College of Social Work, The Ohio State University)

In recent years, the focus of social network theory in behavioral ecology and the social sciences has shifted to understanding the dynamics of social networks. Data analytical methods such as relational state models and others have been used to address patterns of network change over time as agents gain or lose ties and how network structure coevolves with the attributes of agents in real-world networks. Network models are beginning to incorporate data at multiple scales and multiple types of interactions. New technologies have facilitated collection of large quantities of data in many systems allowing increasingly sophisticated analyses of changes in social structure over time.

Mathematical and empirical challenges arise because social networks are complex systems that emerge from, as well as influence, the interacting decisions of multiple, autonomous, objective-maximizing or goal-oriented agents. Agents often have multiple types of relations, resulting in multilayer (multiplex) networks. Current techniques for data analysis of dynamic networks are best suited to address enduring relationships, rather than momentary interactions, but many social interactions are better described by the latter. Consequences of agent decisions to pursue interactions can depend on attributes at multiple levels, and decisions that maximize agent objectives may be in conflict with those of others or with beneficial outcomes for the network as a whole. In humans and non-human animals, opportunities for interaction are constrained by factors such as location and mobility. Social networks frequently involve a small number of agents, and stochastic processes are likely to be important influences on network dynamics. Key emerging problems include how to incorporate multilayer and momentary data into network models, the roles of feedbacks between space use and network processes, how individual