

ANNUAL REPORT DMS-1440386: YEAR 2016-2017

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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

MBI offers a vigorous program of research and education, and fosters the growth of an international community of researchers in this new field.

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 addressed the following scientific challenges in its programming during 2016-2017:

Need to learn the scientist's language: In order to contribute to the solution of problems in the biosciences, mathematicians and statisticians must first learn some science. In particular, they must learn the bio-scientist's language before they can understand the problems clearly enough to bring the power of the mathematical sciences to bear. The continuing rapid pace of research in the biosciences precludes most active biomedical researchers from devoting substantial effort to learning additional mathematics. MBI is actively encouraging mathematical scientists to learn the bio-scientists' language, and to work with them in highly interdisciplinary teams working the boundaries of mathematics and science.

Need to develop new mathematical/statistical models and techniques: While we can expect that established methods in mathematical science will be of immediate use, the quantitative analysis of fundamental problems in bioscience will undoubtedly require new ideas and new techniques. Similar observations apply to diverse research areas across the biosciences ranging from the

study of basic structures in the brain to the expression, regulation, and control of genes. MBI is providing a forum for scientists to begin modeling these systems in ways, which are scientifically relevant yet amenable to analysis that requires skillful approximations and new techniques.

Need to increase the community's size: The current size of the mathematical bioscience community is relatively small compared to the demands of bioscience. MBI encourages the participation of established mathematicians and statisticians in mathematical bioscience and is nurturing a new generation of researchers more systematically than before.

MBI activities mostly fall under five categories (scientific programs, postdoctoral fellows, national impact, education, and diversity) and MBI is developing new programs in each of these categories: workshops, institute partners and mentoring, early career awards and long-term visitors, education programs, and diversity and outreach.

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 2016-2017

MBI hosted two Emphasis Semester programs in 2016-2017: the autumn 2016 Emphasis Semester was on *Analysis of Complex Data in Biological Systems* and the spring 2017 semester was on *Growth and Morphogenesis*.

Autumn 2016 Emphasis Semester: Analysis of Complex Data in Biological Systems

The Organizing Committee for the **Autumn 2016 Semester** consisted of **Konstantin Mischaikow** (Mathematics, Rutgers), **Qing Nie** (Biomedical Engineering and Mathematics, UC Irvine), **Horacio Rotstein** (Mathematics, NJIT), **Terence Speed** (Bioinformatics, Walter and Eliza Hall Institute of Medical Research), **Vladimir Vacic** (Computer Science, UC Riverside), and **Michael Waterman** (Biological Sciences, Mathematics, and Computer Science, USC).

Within the next few years all fields of mathematical biology will be impacted by large amounts of complex data. Because of this, there are many new mathematical questions to be addressed. Should old simple models be thrown out and should we begin again with newer complex models? Or are there mathematical ways to use the new data to determine parameters in the old models more accurately and thus allow their parameters to be updated automatically in real time as the data stream in. These questions are fundamental to medical practice in acute crises, to the dynamical behavior of cells, to policy decisions about vaccination and epidemic spread, to the effects of climate change on ecological niches, and to our understanding of brain function.

Scientists now have huge amounts of data about processes that are only partially known or unknown. The question is: How can we use the data to gain new mechanistic understanding about how biological systems work? Some examples are:

- New techniques in imaging allow the collection of large amounts of patient data. Monitors give huge amounts of data on real time about organ and whole body physiology, as well as microbiomes. We can now understand better how we are different as well as how we are similar, and what consequences these differences have.

- Sensors can track individual animals and reveal complicated changes in ecological environments due to climate change. Cell phones can record geospatial information that can be useful when trying to understand the spread of diseases.
- New techniques allow biologists to observe subcellular behavior in real time.
- Moreover, these data can be connected in important ways. The evolution over relatively short times of pathogens within individuals affects the spread of disease in populations. So population dynamics is related to immune system dynamics.

This MBI emphasis program explored new mathematical techniques used in the analysis of complex data in a variety of biological systems and settings. Fields that can be expected to contribute to the understanding of complex data are combinatorics, probability theory, statistics, geometry, algebraic topology, control theory, and ordinary and partial differential equations.

Autumn 2016 Emphasis Semester Workshops:

1. Second Workshop on Omics Data Analysis (September 6 - 8, 2016)
2. Workshop 1: Topological, Geometric, and Statistical Techniques in Biological Data Analysis (September 12 - 16, 2016)
3. Workshop 2: Models for Oncogenesis, Clonality and Tumor Progression (Sept. 26 - 30, 2016)
4. Workshop 3: Dynamical Systems and Data Analysis in Neuroscience: Bridging the Gap (October 17 – 21, 2016)
5. Workshop 4: Population Models in the 21st Century (November 14-18, 2016)

Spring 2017 Emphasis Semester: Growth and Morphogenesis

The Organizing Committee for the **Spring 2017 Emphasis Semester** on *Growth and Morphogenesis* consisted of **Tomas Alarcon** (Mathematical Biology, Centre de Recerca Matemàtica), **Philip Maini** (Center for Mathematical Biology, University of Oxford), **Frederik Nijhout** (Biology, Duke), and **Pablo Padilla** (Institute of Applied Mathematics, National Autonomous University of Mexico (UNAM)).

Morphogenesis, the origin of form during the development of an organism, constitutes the processes by which simple cellular arrays are transformed into highly structured and often complex tissues, organs and appendages. The mechanisms of morphogenesis are exceptionally complex and diverse, and are only partially understood. There is a large experimental literature on how various genetic, physiological and morphological perturbations alter morphogenesis, but the interpretation of those results is largely done through verbal, conceptual and diagrammatic models. Although such models have an internal logic they are not quantitatively rigorous and typically do not suggest specific mechanisms other than simple single-level biological processes like transcription or translation. Mathematical modeling has played an important role in developing a deeper understanding of the capacities and limitations of various mechanisms. Problems in morphogenesis have also led to the development of new mathematics such as Turing systems and the development of multiscale modeling approaches.

We know that biological function arises from the integration of processes acting across multiple scales. In many cases, these scales are intimately coupled so that a separation of scales is not possible. This leads to the problem of how to couple models of different forms (deterministic, stochastic, agent-based) across scales and also the challenge of how to analyze them, both mathematically and computationally.

To have impact in biology, mathematical models must be validated and then used to make biologically testable predictions, or to help explain biological phenomena. To date, biological data have been quite coarse and rather static (especially in development), so high-level modeling involving partial differential equations has, by and large, been appropriate. However, we are now at the dawn of a new era in which, for the first time, we have spatiotemporal data. Thus the new challenges facing us are:

1. How to collect robust summary statistics from biological data, ranging from expression of biomarkers to the structural changes in the morphology of growing tissues?
2. What is the appropriate level of model description consistent with the data available?
3. How do we integrate multimodal, multiscale data to allow us to determine parameter values in our models and subsequently validate our models?

To achieve advances in these areas requires a broad range of expertise and we held three workshops which brought together experts from a number of different disciplines to present the state of the art in their fields and to work together to arrive at a consensus on what are specific, focused challenges that can be addressed over the next five years.

Spring 2017 Emphasis Semester Workshops

1. Workshop 1: The Biological Challenges in Morphogenesis (February 20-24, 2017)
2. Workshop 2: Modelling of Tissue Growth and Form (March 6-10, 2017)
3. Workshop 3: Hybrid Multi-Scale Modelling and Validation (March 27-31, 2017)

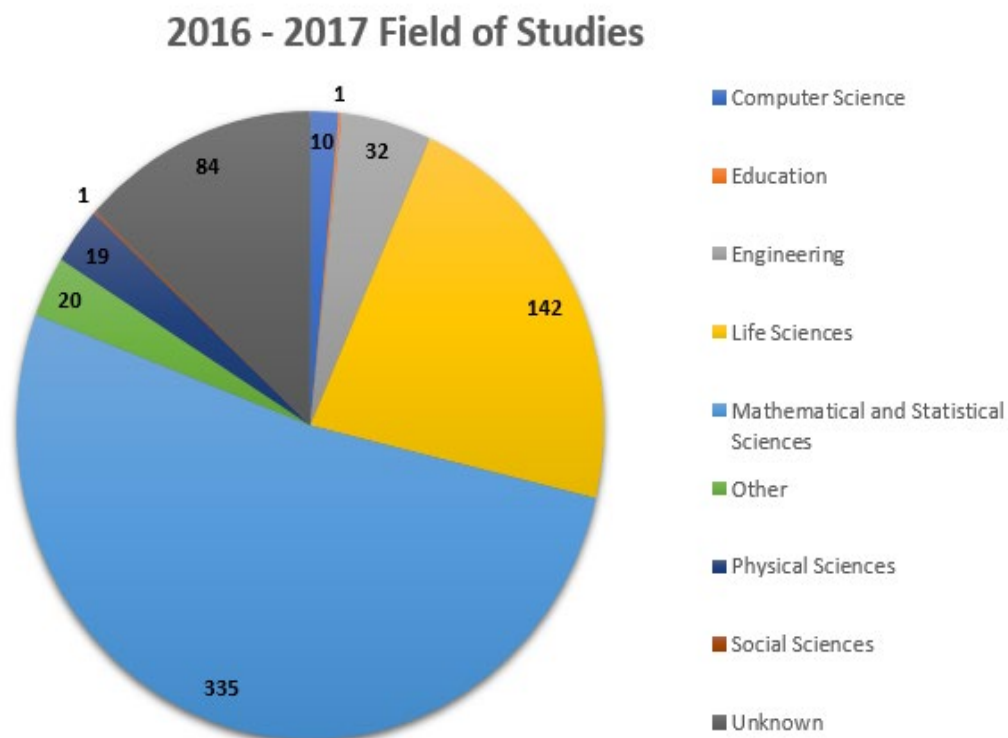
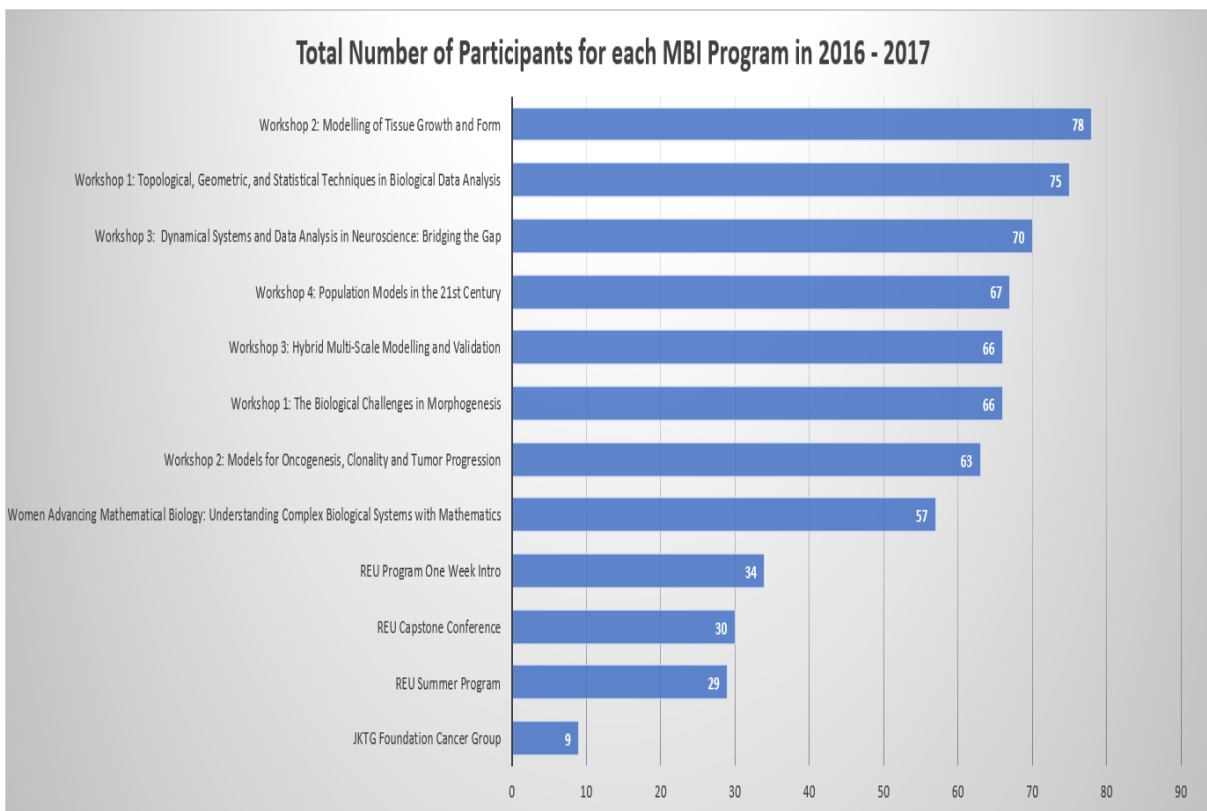
Spring 2017 Current Topics Workshops

1. Women Advancing Mathematical Biology: Understanding Complex Biological Systems with Mathematics (April 24-28, 2017)

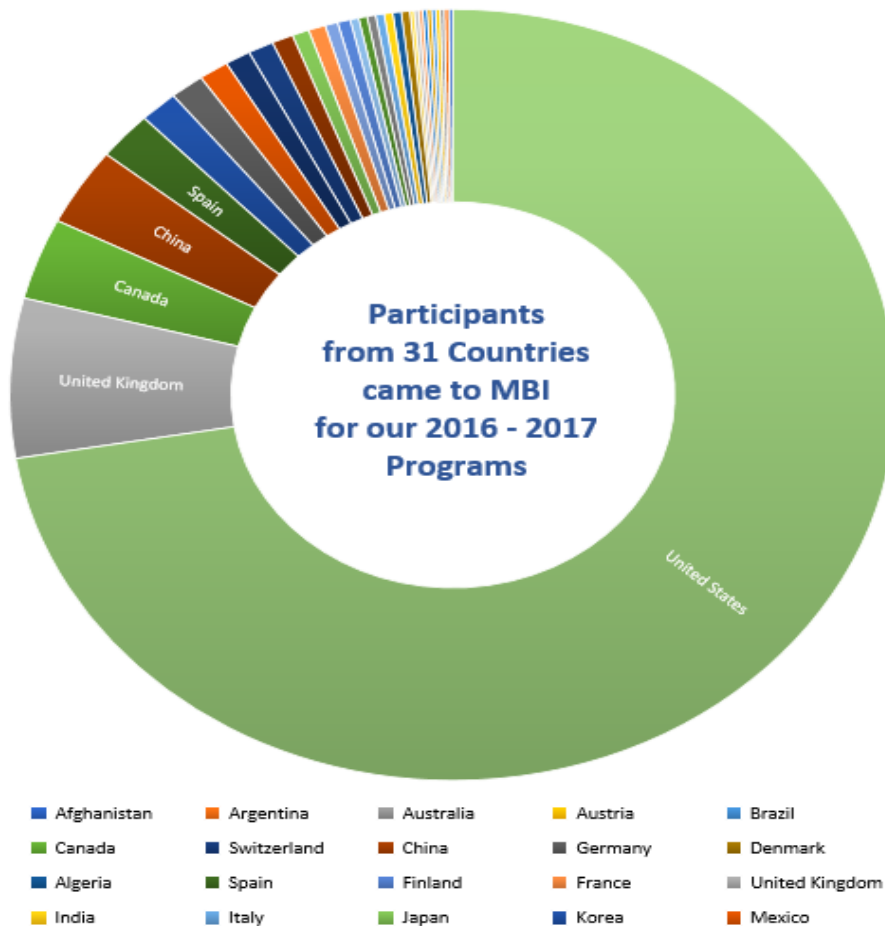
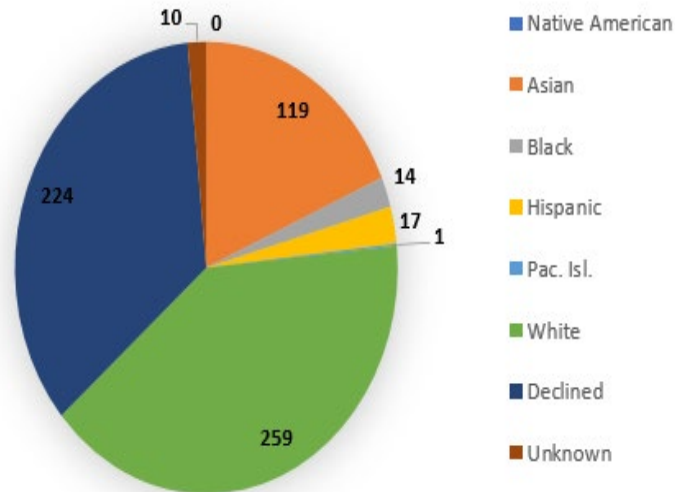
The goal of this workshop was to tackle six various biological and medical questions by using mathematical models for complex system dynamics. Further description is provided in workshop reports section. The workshop was co-sponsored by Association for Women in Mathematics and Microsoft corporation.

PARTICIPANT DATA & DEMOGRAPHICS

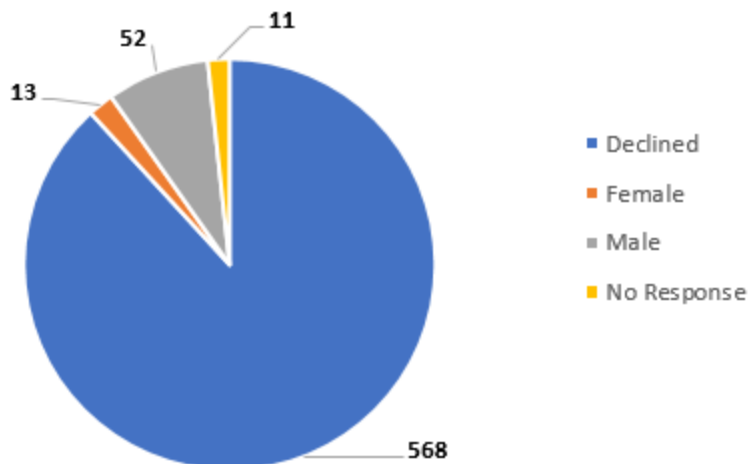
- 644 participants, mentors and speakers took part in MBI's 2016-2017 Programs.
- **A complete list of participant data is attached in the Participant/Organization section of the research.gov online reporting form.**



2016 - 2017 Race & Ethnicity Demographics



2016 - 2017 Gender Demographics



MBI WORKSHOP REPORTS

Autumn Workshop 1 - Topological, Geometric, and Statistical Techniques in Biological Data Analysis (September 12-16, 2016)

Organizers: Carina Curto (Pennsylvania State University), John Harer (Duke University), Konstantin Mischaikow (Rutgers)

Report by: Colby Long, Min Wang, and Yangyang Wang

Monday, SEPTEMBER 12, 2016

Topological analysis of biological data using persistence landscapes

Peter Bubenik (University of Florida)

One approach to combining geometry, topology and statistics in the analysis of data consists of the following steps: (1) use the data to construct a geometric object; (2) apply topology to obtain a summary; and (3) apply statistics to the resulting summaries. However, when the standard topological summary is a persistence diagram, it is difficult to apply statistical tests. In this talk, Dr. Bubenik explained how it is often fruitful to replace the persistence diagram with a vector (or better yet, a point in a Hilbert space). He introduced one such construction with particularly nice properties (e.g. reversibility) called the persistence landscape. The persistence landscape replaces the bar code associated to a persistence diagram with a vector in a Hilbert space. He then presented two applications of the persistence landscape.

The first was to distinguish the conformations of the maltose binding protein found in *E. coli*. It is known from X-ray crystallography that there are fourteen conformations of this protein, seven open and seven closed. Representing each conformation as a set of points and then applying the Čech construction gives a filtered simplicial complex, from which a persistence diagram and persistence landscape are derived. Applying standard statistical methods, the conformations are

clustered into two groups which exactly correspond to those that are open and those that are closed. The second application presented was using persistence landscapes to identify patients with Alzheimer's disease. The persistence landscapes were constructed from images of the hippocampi of several patients. By applying statistical methods to the persistent landscape data, researchers were able to predict the presence of Alzheimer's in patients with 73% accuracy.

Data structures for real multiparameter persistence

Ezra Miller (Duke University)

Some biological data, such as the images of fruit fly wing veins, generate persistent homology with multiple continuously varying parameters. In this talk, Dr. Miller discussed how the statistical analysis of persistence presents fundamental challenges. For example, it is unclear how to encode persistence summaries for automatic computation or how to carry out statistical analyses with the summaries, either theoretically or algorithmically. He then presented joint work with David Houle (Florida State University), Ashleigh Thomas (Duke University), and Justin Curry (Duke University) in which they address these issues. In particular, they have developed an algebraic and geometric framework for approaching these problems that clarifies the topological interpretation of a multiparameter persistence summary. This framework has proven useful for two discrete parameters, but works equally well for continuous parameters or even for filtrations by arbitrary partially ordered sets. The primary objects of their construction are modules graded by vectors of real numbers. They have obtained many results using tools from combinatorial commutative algebra and Dr. Miller presented several conjectures that remain open.

Object Oriented Data Analysis

J. S. Marron (University of North Carolina, Chapel Hill)

Object Oriented Data Analysis is the statistical analysis of populations of complex objects. In this talk, Dr. Marron provided an overview of the field and gave several examples of how persistence methods and topological data analysis have proven useful. As he explained, in modern complex data analyses, the objects of statistical analysis may be vectors, functions, shapes, or even tree-structured objects. These new contexts for Object Oriented Data Analysis create several potentially large new interfaces between mathematics and statistics. The notion of Object Oriented Data Analysis helps focus interdisciplinary discussions by first encouraging the question: What should the data objects be?

To illustrate, Dr. Marron presented a problem in which the data objects were the blood vessel networks in human brains. Eventually, the goal of studying these blood vessel networks would be to detect brain cancer or determine the likelihood of stroke. As a first challenge, he and his collaborators wanted to see if it was possible to determine the age or gender of patients only from their blood vessel networks. He outlined the many approaches they tried, none of which was able to produce the strong correlations obtained using persistence methods. Dr. Marron concluded his talk by summarizing the current state of persistence methods applied to Object Oriented Data Analysis. As he argued, it has clearly been shown that there are situations in which the methods work really well, and one of the key challenges now is understanding precisely what those situations are.

Global dynamics of networks under perturbations of network topology

Tomas Gedeon (Montana State University)

In this talk, Dr. Gedeon discussed a new approach that is used as a platform for qualitative studies of gene regulation. He started by proposing interesting questions on network dynamics from several examples and outlining the framework of the whole talk. Dr. Gedeon then used an example of Hill function model to illustrate why ODE model sometimes may be wrong for modeling cell biology. A more appropriate model called switching model is presented, and its advantage in capturing the phase space is explained by a simple example with collection of walls and target point coordinates plot. He also explained the relationship between the dynamics and Morse graph in general settings and found that the dynamics is essentially a topological representation of Morse graph in the phase space. Furthermore, Dr. Gedeon focused on parameter space and studied the general system where the parameters define the walls in a switching model. He then used combinatorial construction to build the constraints on parameters which correspond to a geometric region in multi-parameter dynamical systems. Dr. Gedeon and his partners also computed a Database for the dynamics, which rigorously approximates global dynamics over the entire parameter space. The results obtained by this method capture the dynamics provably by comparing to data with evidence on dynamical features and patterns of maxima and minima. They applied their approach to study neighborhood of a given network in the space of networks. They started with a E2F-Rb network underlying the mammalian cell cycle restriction point and showed that majority of the parameters support either the GO, NO-GO, or bistability between these two states. Finally, 1000 perturbations of this network are sampled to study robustness of this dynamics in the network space.

Statistical shape analysis of 3D objects using square-root normal fields**Sebastian Kurtek (The Ohio State University)**

Dr. Kurtek presented a novel Riemannian framework for comprehensive statistical shape analysis of 3D objects, represented by their boundaries called parameterized surfaces. Comprehensive framework means tools for registration, comparison, averaging, and modeling of observed surfaces. Registration is analogous to removing all shape preserving transformations, which include translation, scale, rotation and re-parameterization. The framework is based on a specific representation of surfaces termed square-root normal fields and a closely related elastic metric. The main advantages of this method are: (1) the elastic metric provides a natural interpretation of shape deformations that are being quantified, (2) this metric is invariant to re-parameterizations of surfaces, and (3) under the square-root normal field transformation, the complicated elastic metric becomes the standard L2 metric, simplifying parts of the implementation. He then presented numerous examples of shape comparisons for various types of surfaces in different applied areas. He also computed average shapes, covariances and perform principal component analysis to explore the variability in different shape classes. These quantities are used to define generative shape models and for random sampling. Specifically, Dr. Kurtek showcased the applicability of the proposed framework in shape analysis of anatomical structures in different medical applications including endometriosis, Attention Deficit Hyperactivity Disorder and Alzheimer's Disease. He finally summarized the talk with the contribution on developing the comprehensive Riemann framework and discussed his current and future work for shape analysis.

Tuesday, SEPTEMBER 13, 2016

Noise systems and continuous invariants of multidimensional persistence modules

Wojtek Chacholski (KTH Royal Institute of Technology)

In this talk, Dr. Chacholski presented a new perspective on multidimensional persistence for data analysis and introduced a tool for creating numerous new invariants for multidimensional persistence modules. He began by introducing hierarchical clustering on a dataset and explaining the notion of continuity via the map from measurements to persistence sets. He then introduced persistence modules and described why they are better than persistence sets. In his opinion however looking for complete invariants of algebraic objects such as the multidimensional persistence modules is not the main goal of topological data analysis, and it is much more useful to be able to extract out of such modules their continuous features. Dr. Chacholski also provided some fundamental properties of tame and compact functors including the category of tame functors, and showed how to compute certain homological invariants. He then gave the definition of a noise system and used several examples of different explicit noise systems to illustrate how a noise system leads to a continuous invariant. And he explored this further where he looked at under which circumstances a noise system is closed under direct sums. Furthermore, Dr. Chacholski used the noise system to define a metric on tame functors inducing a topology on such functors, and this topology can be used to construct continuous invariant of persistence module. He finally showed that this invariant turns out to be closely related to the well-studied barcode for one-dimensional persistence and an appropriate choice of a noise system.

Topological and geometric tools for modeling shapes and surfaces

Sayan Mukherjee (Duke University)

Dr. Mukherjee mainly talked about two parts of his research: (1) persistent homology transformation for modeling shapes and surfaces, and (2) solving synchronization problem for a collection of objects. In part one, he introduced the topological transform statistic called persistent homology transform (PHT) to model surfaces and shapes without requiring landmarks. This statistic is a collection of persistence diagrams --- multiscale topological summaries used extensively in topological data analysis. He also discussed application of this statistic to represent shapes and execute operations such as computing distances between shapes that are not isomorphic since topological features are used. Furthermore, Dr. Mukherjee outlined how the transform can measure distances between place probability models on shapes and surfaces, and performed the theoretical investigation on injectivity and sufficiency of it. He also used the metric on the space of PHTs and compared PHT with the other methods in analysis of a variety of real datasets. The comparison results suggest that the PHT distances may be outperforming the other methods. In part two, Dr. Mukherjee proposed two different perspectives on solving the synchronization problem which is to learn the transformation between elements within a group of actions. That is, it can be thought of either geometrically in terms of holonomy or in terms of De Rham cohomology theory. With several examples to describe various versions of synchronization problem, Dr. Mukherjee explained his ideas by borrowing the knowledge from potential compatibility on graphs, representation theory, circle consistency, parallel transform procedure, fiber bundle and manifold learning. He also showed that the solution is essentially in the kernel of a Laplacian when formulating the synchronization problem on a graph structure.

Dr. Mukherjee finally gave interesting examples to show algorithms on how to use the solutions for corresponding synchronization problems.

Topological analysis of chromosome conformation capture data

F. Javier Arsuaga (University of California, Davis)

Dr. Arsuaga started his talk by presenting examples of yeast and human to explain that chromosomes are highly condensed in all organisms. He then introduced some theoretical and experimental studies to show that condensation induces topological complexity in the form of knotting and linking. To tackle the problem of condensation, a novel experimental technology called Chromosome Conformation Capture (CCC) is introduced which can measure the proximity of DNA fibers inside the cell and create proximity heat maps for the whole genome of any organism. But the amount of topological information extracted from the data remains to be determined. Therefore Dr. Arsuaga presented two examples, human and yeast, on the topological analysis of Hi-C data. In the example of human genome, Dr. Arsuaga and his collaborators proposed a modified BFACF algorithm, which is a dynamic Monte Carlo method simulating knotted lattice polygons confined in a sphere, to demonstrate that the contact frequencies of these polygons agree with the Hi-C data. And the simulation shows that the celebrated fractal model, which implies topological simplicity, is one of many possible models that can explain the CCC data. In the yeast example, they proposed that multiple reconstruction approaches from geometrical and topological perspectives can be inferred from the yeast datasets, and showed how the Rabl configuration of chromosomes in the yeast cell simplifies the topology of the otherwise highly entangled genome.

Approximations of complex networks underlying cancer biology

Monica Nicolau (University of California, Davis)

New technology helps collecting more information but has also generated data that are hard to analyze mathematically. To resolve these challenges, efforts on modifying and adapting traditional mathematical tools as well as developing novel techniques to tackle the data analysis problems are required. In this talk, Dr. Nicolau firstly introduced Progression Analysis of Disease (PAD), an approach to data analysis of disease that unravels the geometry of data sets and provides an easily accessible picture of the outcome. This method relies on a combination of two mathematical methods of analysis of large data sets: (1) Disease Specific Genomic Analysis (DSGA), a method that identifies the component of data consistent with disease, by defining a transformation that measures the extent to which diseased tissue deviates from healthy tissue; and (2) Mapper, a mathematical tool that extracts continuous progression drifts from the data. As an example, she applied PAD to analyze breast cancer transcriptional microarray data. Afterwards, she discussed methods to tackle computational challenges involving smoothing and sequential approximations to the complex networks underlying data from biological systems. One of the methods introduced by Dr. Nicolau is how to smooth out adjacency matrix of the real data so that it collapses to a small network which still captures important features of the original network. At the end, she discussed applications to problems from biological high throughput data analysis, e.g. how can people understand the complex network underlying HiC data by a sequence of progressive simplifications of the network/adjacency matrix.

Stable local homology and QTL analysis of plant morphology

Washington Mio (Florida State University)

One of the biggest problems involved in data is to understand the organization of the total data sets. If the data is complex, then normally it carries rich geometry and so the organization needs to be uncovered. Persistent homology is a powerful technique for tackling this problem by probing and analyzing the shape of data with complex distributions and has been widely used in studies of global organization of data across spatial scales. Much richer information can be uncovered through local and regional topology, however, naive localization is prone to instabilities as localization can be extremely sensitive to sampling and noise.

With the primary goal of discovering interpretable associations between genotypes and complex phenotypes to elucidate the genetic basis of plant morphology, Dr. Mio presented an approach to local homology that is provably robust and discussed how it may be used in shape analysis. He firstly talked about the scale-space representation of data. With data sets in leaves as an example, he showed how the data can be converted into functions, which provides a path to stability and robustness. Then he discussed the local homology at a fixed scale as well as across scales, which is viewed as a path of barcodes or persistence diagrams that is stable with respect to the Wasserstein distance. While starting with the case of Euclidean data, he also included the reinterpretation and extension to data on other metric spaces in this talk. At the end, Dr. Mio presented quantitative trait loci analysis of tomato leaf shape. Applications of this research consist of studies of the genetic basis of variation in plant morphology, finding associations between genotypic and phenotypic variation, morphological changes during cellular development and differentiation, genome wide association study of human facial shape, and so on.

WEDNESDAY, SEPTEMBER 14, 2016

Exploring the structure and function of biological clock networks**Steve Haase (Duke University)**

Gene regulatory networks (GRNs) can drive cyclic and temporally ordered processes in biological systems. One of the best-known GRNs of this type is the circadian clock, which drives rhythmic behaviors with a period of approximately 24hrs. The mammalian circadian clock controls many bodily functions such as core body temperature, heart rate, blood pressure and so on. The circadian clock network controls periodic functions, in part, by regulating a dynamic program of gene expression where substantial fractions of the genome are expressed during distinct phases of the circadian cycle.

Dr. Haase and collaborators have observed that the cycling time periods for different organisms, separated by many millions of years of evolution, have different time scales. However, gene expression programs for different organisms are strikingly similar, which suggests that a class of GRNs may serve as central mechanisms that drive temporal gene expression programs in biological systems. To identify the structure and function of these networks, he took the budding yeast cell as one example. Dr. Haase described experimental and quantitative approaches aimed at probing the dynamics of a GRN that controls the well-ordered, periodic program of transcription observed during the yeast cell-division cycle. He showed that a network of sequentially activated transcription factors (TF) functions acts as an underlying oscillator for cell-cycle in yeast. By examining the individual contributions of a TF network and cline-CDKs to the maintenance of cell-cycle oscillations, he discovered that while cyclin-CDKs are not

required for oscillations, they do contribute to oscillation robustness and serve as regulators and effectors of oscillations driven by a TF network. He also demonstrated that transcriptional oscillations are driven by a complex interconnected network. Further, he discussed a new approach, the local edge machine, for inferring the structure of these GRNs directly from time-series transcriptome data.

Time for precision medicine: from big data to novel therapeutics

John Hogenesch (Cincinnati Children's Hospital Medical Center)

Most organisms on the planet have clocks. This internal clock drives oscillations in a diverse set of biological processes. In this talk, Dr. Hogenesch discussed investigating the impact of circadian time in animals and people on how therapeutics work. The suprachiasmatic nuclei (SCN) of the hypothalamus comprise the central pacemaker, integrating environmental cues and coordinating peripheral oscillators throughout the body. Dr. Hogenesch explained the mammalian circadian molecular oscillator mechanism which is based on the interactions between two transcriptional/translational feedback loops. This mechanism governs circadian output rhythms in all cells throughout the body, but there are tissue-specific differences. To further understand this, Dr. Hughes and his collaborators designed an experiment on mice and observed 43% of all protein coding genes showed circadian rhythms in transcription somewhere in the body, largely in an organ-specific manner. Moreover, Dr. Hogenesch and his collaborators explored the potential medical impact of circadian genes as drug targets and disease-associated genes. They found a majority of best-selling drugs in the United States target circadian gene products. Many of these drugs have relatively short half-lives, suggesting the potential impact time of administration could have on their action. Finally, he talked about developing a method that allows population level analysis of human data and applying it to human frontal cortex, lung, liver and blood.

Topological graph theory in DNA self-assembly and DNA recombination

Natasha Jonoska (University of South Florida)

Understanding the nature of self-assembly is becoming one of the most essential questions in science and technology. In this talk, Dr. Jonoska introduced several tools they built and experimental designs regarding DNA based self-assembly, with their applications on DNA origami. Genome rearrangement and DNA recombination processes can be modeled as 4-regular spatial graphs with rigid vertices, called assembly graphs. Dr. Jonoska talked about a finding that each multigraph can be designed in such a way that a single circular molecule traverses each edge of the graph at least once. Such reporter molecule could further be used to identify the assembled molecular structure. This is also useful in identifying the DNA structure assembled as a result an instance of solution to a three-colorability problem.

Dr. Jonoska also introduced how DNA duplex and junction molecules can form two dimensional arrays as well as three dimensional structures. There have been recent studies on the creation of DNA origami polygonal meshes on the nanoscale. However, designing meshes of three dimensional structures without knotting still remains as an open question. As a final remark, Dr. Jonoska pointed out their goal to better understand the intrinsic principles of self-assembly.

Persistent Homology of Directed Networks via Dowker Filtrations

Facundo Memoli (The Ohio State University)

Networks are ubiquitous in many fields, including biology, sociology, and economics. In this talk, Dr. Memoli presented methods for computing two network features with topological underpinnings: the Rips and Dowker Persistent Homology Diagrams. The goal of computing these network features is to try to extract information from the network and develop reasonable means of clustering networks exhibiting similar properties. The formulations work for general networks, which may be asymmetric and may have any real number as an edge weight. This is a valuable feature, as many of the standard methods for data analysis on networks do not apply to asymmetric networks.

Both constructions take a network and produce a nested sequence of simplicial complexes. The resulting complexes have topological features and so are subject to the methods of persistent homology. Dr. Memoli explained the constructions in detail and discussed the theoretical stability properties of both the Dowker and Rips persistence diagrams. Stability is important, since for applications, it is desirable that two networks that are close in some metric produce complexes that are also close. Finally, he alluded to some experimental results, in joint work with his Ph.D. student Samir Chowdhury, on a variety of simulated and real world datasets using these methods. In particular, they applied both methods to a classification task on a database of networks to determine when each method performed best.

Persistent vs. Consistent Homology from Point Clouds

Tim Sauer (George Mason University)

Persistent homology has become a standard tool in modern data analysis. The idea is to identify homological generators at various scales as a parameter representing distances between points is increased. In this talk, Dr. Sauer showed that for general sampling from a Riemannian manifold, there is a graph construction that captures all topological features in a single graph. More precisely, the graph converges spectrally to the Laplace-De Rham operator of the manifold in the limit of large data. The graph construction, called continuous k-nearest neighbors (CkNN), neutralizes nonuniform sampling and in practice reduces data requirements as well. In addition to describing the construction, Dr. Sauer presented joint work with Tyrus Berry in which they examined under which circumstances their “consistent” homology approach is preferred to persistent homology.

One of the applications they discussed was determining the patterns of repetition in a video of an oscillating spiral. They first encoded frames of the video as points in a high-dimensional Euclidean space and then applied persistent and consistent homology to these point clouds. They showed that their CkNN construction implied a manifold topologically equivalent to a torus. This is precisely what one would expect as the torus exhibits periodicity in both its spin and oscillation. However, with persistent homology methods, it was impossible to choose a parameter that produced the expected topology from the point cloud data. This example was one of several that illustrated how the consistent approach may prove useful for detecting low-dimensional dynamics.

Thursday, SEPTEMBER 15, 2016

Topological Lenses for Spatially Embedded Networks

Chad Guisti (University of Pennsylvania)

The human brain is a massively complicated network and uncovering the structure of this network is a central challenge of neuroscience. In his talk, Dr. Guisti described how topological methods can be applied to brain images to reveal fundamental connections between structures in the brains. In order to gather data, researchers first use diffusion spectrum imaging (DSI) which reveals the patterns of fluid flow throughout the brain. They then construct a weighted network where each node corresponds to a functional region of the brain. The weights between the nodes of the network are determined by the number of streamlines between regions as detected by the DSI. Dr. Guisti and his collaborators apply persistent homology to the resulting networks to explore patterns of connectivity in the brain. They threshold edges by weight and study the resulting sequence of graphs as the threshold is increased.

One feature that they are interested in are the cliques in each graph. Under the minimum energy hypothesis, the brain prefers short, energy efficient connections, and so cliques must be important to be redundantly connected. They also study the homology of the resulting graphs. Interestingly, Dr. Guisti explained how each of the cycles that they detected corresponds to a structure in the brain known to serve an important function. The fact that these cycles also appeared when they studied the networks from different brain scans and different individuals suggests that topological methods are actually detecting essential features of the brain network.

Convex codes, Dowker complexes, and detecting hidden network factorizations

Vladimir Itskov (Pennsylvania State University)

A convex code is a subset of the power set of the set of n elements that arises from intersection patterns of convex sets in a Euclidean space. Despite their natural definition, these codes have not been studied until very recently, motivated by applications in neuroscience. Many neural systems generate patterns of neural activity that can be characterized mathematically as convex codes. These codes reflect topological features of the underlying stimulus space, some of which can be inferred using existing TDA methods. Perhaps surprisingly, not all codes can be realized by a convex cover, and the problem of determining which codes are convex is still open.

Dr. Itskov began his talk by presenting some of the recent results on convex codes. For example, there are certain types of codes, such as those that are maximum intersection complete, that are necessarily convex. He also discussed some bounds on the embedding dimensions of convex codes. The minimal embedding dimension of the code is relevant because it carries information about the stimulus space. He also discussed another class of codes called hyperplane codes in which the convex sets are half spaces of a Euclidean space. As he showed, hyperplane codes are closely connected to the problem of detecting a feedforward network factorization using Dowker complexes. The talk concluded with an example on simulated data that demonstrated how homological invariants can be used to detect these non-linear factorizations.

Two examples of application of topological methods in neuron data analysis

Yusu Wang (The Ohio State University)

Dr. Wang began by introducing an interesting example of neuron cell structure and stating the importance of understanding neuron structures. She then described two of her recent efforts on analysing neuron structures via topological methods and these corresponded to two topics: (1) neuron structure comparison, and (2) neuronal morphology reconstruction. In the first topic, Dr. Wang described the related work on neuron structures and demonstrated their advantages and

drawbacks from the aspects of efficiency and discriminative power. She then discussed a persistence-based feature vectorization framework and presented the neuron shape comparisons via persistent homology which provides a way to summarize an input domain and the lengths of a specific filtration in the domain. She also showed how the persistence diagram summary can be used to compare neuron trees. The second topic is the neuron reconstruction procedure based on Morse theory. With the related work and main challenges of previous methods introduced, Dr. Wang proposed a framework to automatically extract neuron tree structures from 2D or 3D images with the help of discrete Morse theory. And her idea comes from the finding that neuro structure tends to correspond to ridges of mountain illustrated in an example for the smooth case of Morse theory. She finally gave some preliminary results in each of these two directions.

Homological features of brain functional connectomes show dynamical compensation of age-related structural brain connectomes changes
Francesco Vaccarino (Politecnico di Torino)

In this talk, Dr. Vaccarino explored the characteristics of functional brain networks from a novel perspective that highlights the role of inhomogeneities in the fabric of functional connections. This is done by focusing on the features of a set of homological cycles associated with the weighted functional network. He first gave two simple network examples in natural and societal systems, and constructed a simplicial filtration of the datasets. He then studied the change of the topological structure along such filtration which provides a measure for the topological features emerging across different scales. The complete topological and weight information are preserved and the special mesoscopic structure called weighted network holes are able to be focused on. He obtained that the statistical features of weighted network holes essentially yield a two-classes classification problem and these weighted holes can be uncovered via persistent homology of the weighted clique rank filtration, which recovers complete and accurate long-range information from noisy redundant network data. Furthermore, Dr. Vaccarino considered neuroimaging data coming from functional magnetic resonance imaging, and derived the combined structure and weights in a weighted network. He then leveraged the detected topological information --- generators in the first persistent homology group to define the homological scaffolds. And two types of scaffolds based on persistence and frequency are constructed which highlight the role of links and the number of cycles respectively. He applied the tools to compare resting-state functional brain activity in 15 healthy volunteers after intravenous infusion of placebo and psilocybin. The results show that the psychedelic state is associated with a less constrained and more intercommunicative mode of brain function, which is consistent with descriptions of the nature of consciousness in the psychedelic state.

Using discrete recurrent neural networks to learn structure in recordings of large ensembles of nervous activity

Christopher Hillar (University of California, Berkeley)

Dr. Hillar began his talk by introducing the history and background of the discrete recurrent neural networks (DRNNs). He then described the Hopfield network which is a binary form of DRNN in modeling memory and collective processing of networks of abstract McCulloch-Pitts neurons. With the exponentially increasing storage and tractable advances in training large-scale

networks, the Hopfield networks are now possible to be used widely for special cases of patterns and connectivity structures. He also introduced a learning technique called minimum probability flow (MPF) in Hopfield networks for fitting parameterized distributions, and presented the geometric intuition to optimize the MPF objective function. Furthermore, Dr. Hillar reported a novel, scalable use of DRNNs for the unsupervised discovery of structure in high-dimensional recordings of nervous tissue. He presented two case-studies in detail using the technology: (1) clustering of reoccurring spatiotemporal patterns in spike trains, and (2) denoising microscopy recordings of slices of neural activity. He also trained the Hopfield networks on discretization of grayscale digital photographs using MPF. After training, he demonstrated that these networks have exponential memory capacity, allowing them to perform state-of-the-art image compression in the high quality regime. The encouraging findings suggest that the local structure of images is well-modeled by the binary recurrent neural network. Finally, Dr. Hillar explained how to perform this analysis on standard hardware using the open-source package HDNET, which provides efficient DRNN tools for experimental neuroscientists.

FRIDAY, SEPTEMBER 16, 2016

Geometric combinatorics and RNA branching

Christine Heitsch (Georgia Institute of Technology)

In this talk, Dr. Heitsch introduced an approach of utilizing the ideas from geometric combinatorics to generate the RNA secondary structure from its primary sequence. The traditional prediction based on calculating the minimum free energy is ill-conditioned, meaning that a slight change in thermodynamic parameters would have a large impact on the prediction accuracy. To advance knowledge of the structure, energy trade-offs are investigated among its loop structures with different degrees of branching. In the study of understanding how an RNA viral genome can fold into the dodecahedral cage observed from experimental data and predict the proper secondary structure, Dr. Heitsch introduced an abstraction approach of converting the folded sequence to a weighted plane tree associated with loop energies, and showed that the total energy is minimized by maximizing the number of vertices of degree two. Furthermore, Dr. Heitsch also talked about a new computational framework of parametric analysis of RNA branching configurations, based on the construction of an RNA polytope, whose vertices correspond to RNA secondary structures with common branching. The polytope and its normal fans can then be used to study the effect of varying parameters in the free energy model and help finding the optimal structure.

Mathematics is the champion of biomolecular data challenges

Guowei Wei (Michigan State University)

Biological research is transforming to quantitative disciplines with mathematically driven advances in recent years. Specifically, topology provides a dramatic simplification in analyzing biomolecular data with applications to drug design, protein folding, etc. In this talk, Dr. Wei introduced several previous works they have published on geometric modeling, molecular topological fingerprints and graph theory modeling, with the help of the tools from differential geometry/topology and machine learning. He showed several results to prove the advantages of mathematical approaches in molecular bioscience and biophysics, for instance, comparing the Pearson correlations in protein-ligand binding affinities prediction, their “Feature Functional Theory – Binding Predictor” outperforms all the other eminent methods in molecular biophysics.

Dr. Wei also presented how persistent homology bridges between geometry and topology together, and offers an effective strategy for biomolecular analysis. In another example he demonstrated, with the extension to higher dimensional and multiscale persistence, more topological details can be observed in the modeling of protein unfolding. In addition, with the combination of support vector machine technology in machine learning, they have developed a molecular topological fingerprint classifier which achieved high accuracy in four different types of proteins classification problems.

Hypothesis tests for complicated spatial structures using persistent homology

Jessi Cisewski (Yale University)

Complicated spatial structures (CSS) are common in biological data (e.g. fibrin clots, fibroblasts), but are difficult to quantitatively analyze without losing important information. Topological data analysis (TDA) provides a way for biologists to better understand, visualize, and interpret such data. It has the potential to dramatically improve the analysis of biological data by retrieving and quantifying crucial information that is missed in ad hoc methods by specifically targeting shape-related features. In her talk, Dr. Cisewski showed how she and her collaborators have applied these methods to complicated spatial structures arising in astrophysics. The similarity of these structures to several biological structures suggests that similar methods may be applied there.

Her method involves developing a framework for hypothesis testing of CSS using persistent homology. The randomness in the data (due to measurement error or topological noise) is transferred to randomness in the topological summaries, which provides an infrastructure for inference. These tests allow for statistical comparisons between CSS. One of the novelties of her approach is to first smooth the data and then using level sets of the smoothed data instead of applying the Rips construction directly to the point cloud. This significantly reduces the computational complexity of the problem. She presented several possible test statistics using persistence diagrams and discussed the performance of each as applied to simulated data. In the particular data sets she considered, the Euler characteristic proved to be the most effective test statistic for identifying the underlying parameters that produced the data.

Autumn Workshop 2 - Models for Oncogenesis, Clonality, and Tumor Progression **(September 26-30, 2016)**

Organizers: Marcin Imielinski (Weill Cornell Medical College, Cornell University), Elli Papaemmanui (The Elli Papaemmanuil Lab, Memorial Sloan-Kettering Cancer Center), Raul Rabadan (Department of Systems Biology, Columbia University), Ben Raphael (Computer Science, Princeton University)

Report by: Jeff Gaither, Leili Shahriyari, Casper Woroszyllo

MONDAY SEPTEMBER 26, 2016

Stochastic evolutionary modeling of cancer development and resistance to treatment

Ivana Bozic (Harvard University)

Dr. Bozic started her talk by saying cancer is the result of evolutionary process. She mentioned that there are a lot of heterogeneities in tumors. Not only there are heterogeneity the same cancer among different patients, there is also heterogeneity in the tumor of a single patient. The majority of mutations are not drivers while presenting the frequency of mutations for various types of cancers. Why do we care about heterogeneity: it is because heterogeneity leads to the resistance to the therapy. There are two options: resistant cells were existed before treatments, or they have been created during treatments. They have tried to answer if the resistant cells were pre-existed. They predicted one cell in million cells is resistant.

The speaker explained the model developed by Luria & Delbruck 1943 to answer is resistance adaptive or genetic. To understand the heterogeneity of resistant cells, she developed a model by generalizing Luria-Delbruck model. They calculated the number of resistant mutants and their distributions. As a result, resistances not due to a single resistant clone. They have also compared their results with experimental data.

She also presented a model for clonal kinetics during targeted therapy in CLL. She developed a stochastic model for neutral evolution during clonal expansion. At the initial time of the model there is a single mutation, and they look at the order of clones that are generated. They calculated the expected number of clonal and subclonal mutations. All the models, which were provided in this talk, were non-spatial models. She ended her talk by a brief explanation about her new spatial model.

Bayesian inference of positive and negative selection in human cancers in light of mutation heterogeneity

Shamil Sunyaev (Harvard University)

Dr. Sunyaev started his talk by explaining the goals of using cancer genomics. Most gene mapping methods (linkage association) rely on recombination and are only applicable to sexual systems. The method that we have is identifying selected genes/functional units by recurrence. This signature of selection is completely confounded by mutation rate variation. However, “non-functional” regions may not serve as an ideal null model if mutations rate is correlated with “functionality”.

Somatic cancer mutation density is associated with replication timing. The idea is that if there are DNA damages, there are two decisions repair DNA or mutation occurs. There are many associations between DNA repair system and the frequency of mutations. He showed that mutations depend on the cell type of origin. They looked at the cluster of mutations for various types of cancers. He concluded that the precisely estimating local mutation rate is very difficult. He then mentioned that the errors of local mutation rates estimate amplifying for extreme outliers that masquerade as genes under selection. Then, he explained his model; he assumed mutations have Poisson distribution. They fitted the model by combining 17 cancer types. He concluded that the number of cancer drivers is limited, and negative selection in cancer is weaker than in any other biological context. He then modified his model to analyze the individual genes to find cancer drivers.

Tracing the origin of disseminated tumor cells in breast cancer using single-cell sequencing **Peter Van Loo (The Francis Crick Institute)**

Dr. Van Loo started his talk by mentioning genomes of cancer cells are very messy, and cancer evolves because of the occurrences of mutations. He explained that the driver mutations result in intra-tumor heterogeneity. He then discussed the process of metastasis, and disseminated tumor cells in breast cancer (DTCs).

They study DTCs in bone marrow and want to find the origin of DTCs using experimental models. They have used immune-cytochemical techniques to identify DTCs, as well as single cell sequencing of the primary tumor and the DTCs in the bone marrow. They have identified some un-known origin cells in the bone marrow of breast cancer patients. There was a breast cancer patient that did not have a single DTC from a primary tumor; this might be the result of the limitations of experimental methods. In one patient they found that the origin of the DTCs were in the lymph-node metastasis. Dr. Van Loo and his collaborators also observed that most of DTCs were tumor cells. They then studied the aberrant cells of unknown origin and their hematopoietic lineage. They have applied the Battenberg algorithm to SNP6 data to trace DTC origins. As a result, DTCs drive from the MRCA, not the sub-clone. They also found that single cells can resolve the tree. They have concluded that dissemination occurs mostly from sub-clones in an axillary lymph node.

Computational dissection of intra-tumor genetic heterogeneity and applications to the study of cancer treatment, evolution, and metastasis

Scott Carter (Broad Institute)

Dr. Carter started his talk by explaining the future of cancer genomics on 2016. He mentioned that the reason for not having metastatic cancers sequenced, it is because it is hard to get metastatic tissues. Dr. Carter then said that, in the near future, every patient will have right to demand that their genomic data and clinical outcome data be shared, and data will exist in the cloud. He then explained the metastatic breast cancer project “MBCproject.org”. He mentioned that we would sequence 100K metastatic cancers using Liquid biopsy (e.g. blood, urine, CSF).

Dr. Carter then explained the clonal theory of somatic cancer evolution. He said their goal is to deconvolve cancer tissue samples. After that, he introduced his algorithms: CAPSEG and Allelic CAPSEG. He also provided the results of comparing some available methods, EXPANDS, CHAT, SEQUENZA, ACONV, etc.

In the next part, the speaker described that treatments of CLL with chemotherapy result in more aggressive sub-clones to emerge. He also showed a data for metastatic patients: they have observed that 84 out of 88 cases demonstrated unknown connections with primary tumors. Moreover, four out of 88 patients had completely unrelated primary and metastatic tumors. He explained several cases of breast cancer patients with brain metastasis. He also showed a case that the brain metastasis happened in a distant region from the surgically removed metastatic tumor. He ended his talk by the following question: How can we connect Genetics diversity and the phenotypic diversity?

Reconstructing cancer progression models based on probabilistic causation models

Marco Antoniotti (University of Milano - Bicocca)

Dr. Antoniotti discussed algorithms his group has developed for reconstructing cancer progression models both from aggregate, population level data (e.g. TCGA) as well as individual level data

(single tumor or single cell). The key to these algorithms is the notion of probabilistic causation in the spirit of Suppes' causality theory. In the context of biological systems and cancer progression, the notion of causality can be interpreted as the notion of "selective advantage" of the occurrence of a mutation.

Dr. Antoniotti also discussed validation and performance of their algorithms. The algorithms are found in a R BioConductor package "TRanslational ONCOlogy" (TRONCO), which is part of "Pipeline for Cancer Inference" (PiCnIc). This was used to analyse Colorectal Cancer (CRC) data from TCGA. This work highlighted possibly biologically significant patterns in the progressions inferred. In the future, Dr. Antoniotti hopes to move towards individual level analyses, i.e. multiregion and single cell inference.

Quantifying the evolutionary dynamics of human tumor progression
Christina Curtis (Stanford University)

Dr. Curtis discussed the big bang model for human tumor progression and showed that this provides a quantitative framework for understanding tumor progression with numerous clinical implications. In the model, she discussed that the timing of a mutation is the primary determinant of its frequency as opposed to strong selection. Although weak selection is detectable, it is insufficient to alter subclonal architecture. Most detectable ITH occurs early. Late arising, but potentially aggressive subclones may go undetected and yet provide a rich substrate for the emergence of resistance under treatment selective pressure. Some tumors maybe be born to be bad wherein invasive potential may be specified early.

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Dr. Curtis also outlined future directions towards a quantitative understanding of tumor evolution. She mentioned we must first characterize the various modes of primary tumor growth dynamics; this also has implications for delineating the 'drivers'. A "null" (neutral) model is instructive in allowing one to make testable predictions, whereas selection is far more complex. Modeling needs to move towards a more hybrid stochastic and deterministic flavor with densely sampled genomic data. The development of predictive evolutionary models is crucial for advancing precision medicine, but stochastic effects pose limitations.

Evolution of metastases
Johannes Reiter (Harvard University)

Dr. Reiter discussed the evolution of metastases in cancer. In particular, he discussed how temporal, spatial and evolutionary rules governing the seeding of metastases at spatially distinct sites distant from the primary tumor have mostly remained undetermined. He discussed analysis

of 26 metastases and 55 primary tumor regions from 4 pancreatic cancer patients. Based on a Bayesian inference model and Integer Linear Programming, Dr. Reiter designed a new method, Treeomics, to infer metastatic seeding patterns. Using a combination of phylogenetic and sequencing approaches, Dr. Reiter demonstrated that individual metastases were derived from spatially and genetically-distinct subclones within the same primary tumor. However, he also found that the identical driver gene mutations were present in every metastatic lesion of each patient studied.

TUESDAY SEPTEMBER 27, 2016

Non-coding genetic variation in cancer

Ekta Khurana (Cornell University)

Dr. Khurana started her talk by defining non-coding regions and function effects of sequence variants. She emphasized that non-coding RNAs play a crucial role in cancer, and most variant are in non-coding regions. She mentioned that mutations could cause loss and gain of transcription factors motifs. Her group has observed increased density at TF binding sites in melanoma and lung cancer.

Identifying non-coding variants associated with cancer is the goal of the study.

Dr. Khurana then talked about their developed method, FunSeq, to identify variants and mentioned it is important to identify non-coding categories, which are under very strong coding-like selection. She used composite driver for detecting driver coding and noncoding elements. Then, she presented the results for 40 lung adenocarcinomas and 188 prostate cancer samples. She mentioned that we have not identified as many non-coding drivers as we thought. At the end of the talk, she explained their method to inference prostate regulatory network.

Signature of mutational process in human cancer

Ludmil Alexandrov (Los Alamos National Laboratory)

Dr. Alexandrov started his talk by emphasizing that somatic mutations occur on all normal and cancer cells. The simplest mutation is a single mutation in one nucleotide. If we look at the skin cancer most p53 mutations are C to T, and in lung cancer is C to A. He mentioned the process of transforming from fertilized egg to cancer. Then, the speaker talked about using non-negative matrix factorization (NMF) to classify the base substitution mutations. Extracting mutational signature from human cancers show that C to T is the most common single substitution mutations. The speaker presented the results for breast cancer and stomach cancer.

In the next part Dr. Alexandrov talked about the process that tobacco smoking induced carcinogenesis. He investigated the contributions of mutational signatures to smoking induced and non-smoking associated lung cancers. The frequency of mutations is much lower for life-long non-smokers comparing to tobacco smokers. At the end he presented the mutational signatures for various types of cancer for nonsmokers and smokers.

Knowledge-based analysis of mutation signatures reveals mechanistic details of mutagenesis

Dmitry Gordenin (NIH)

Dr. Gordenin combined mechanistic and bioinformatics approaches to understand mutation processes operating in genomes. He used a yeast model to generate hypotheses and apply these hypotheses to tumors. He mentioned that mutagenesis in a variety of single strand DNA intermediates can form cluster of strand-coordinated mutations. He showed that mutation clusters do occur in human cancers. He discovered an endogenous strong mutagen (up to 70%) in many human cancers.

Dr. Gordenin presented the correlation of the mutation density combined signature 2+13 (provided by the previous speaker, Dr. Alexandrov) with an estimated number of APOBEC-induced mutations calculated based in enrichment value for bladder cancer. The speaker showed that even small C- or G- strand-coordinated clusters are highly enriched with APOBEC mutation signature. He presented the results for APOBEC mutation pattern on abundant in cervical, bladder, head and neck, breast, and lung cancer types. He hypothesized that APOBEC mutations occur in the background of many cancers. Dr. Gordenin then presented the anti-correlation of APOBEC mutation load and “time to death” in TCGA bladder cancer for 393 samples. Dr. Gordenin mentioned that yeast system reporting mutagenesis in ssDNA allowed to identify common and specific components of A3A and A3B mutation signature.

Somatic mutations accumulate during the lifetime of a person to environmental and endogenous factor. They discovered that 1000 somatic base mutations in the normal skin of two donors who were highly exposed to UV. As a result, UV induces C to T mutations a di-pyrimidine context, and T to C mutations in a TT context. At the end of his talk, he emphasized that we need common language for expressing hypotheses: mutation load, frequency, rate, motifs, signatures, pattern, spectra, etc.

Mutational signatures reveal the processes underlying cancer evolution

Paz Polak (Broad Institute)

Dr. Polak started his talk by emphasizing that there are mutations in normal tissues, but tumors have a much higher number of mutations. He mentioned the procedure for identifying the somatic mutation lists. The main task is to identify patients who will respond to treatment.

The speaker mentioned that somatic ERCC2 mutations correlate with cisplatin sensitivity in muscle-invasive urothelial carcinoma. ERCC2 is nucleotide excision repair helicase. ERCC2 is significantly mutated gene in bladder cancer. However, somatic ERCC2 mutation is rare for other type of cancers.

The speaker used Bayesian nonnegative matrix factorization to identify signature mutations. Dr. Polak applied this method on TCGA bladder cancer (n=130). As a result, ERCC2 is the only gene highly associated with increased signature 5* activity. They also found that ERCC2 mutations cluster in the helix domain. He concluded that ERCC2 mutations are likely early events and driving clonal signature 5 mutations. Moreover, signature 5* closely resemble COSMIC signature 5, which has been identified in all tumor types.

RAG mediated instability in ETV6-RUNX1 ALL

Elli Papaemmanui (Memorial Sloan-Kettering Cancer Center)

The ETV6-RUNX1 fusion gene, found in 25% of childhood acute lymphoblastic leukemia (ALL), is acquired in utero but requires additional somatic mutations for overt leukemia. Dr.

Papaemmanui used exome and low-coverage whole-genome sequencing to characterize secondary events associated with leukemic transformation. RAG-mediated deletions emerge as the dominant mutational process, characterized by recombination signal sequence motifs near the breakpoints; incorporation of non-templated sequence at the junction; ~30-fold enrichment at promoters and enhancers of genes actively transcribed in B-cell development and an unexpectedly high ratio of recurrent to non-recurrent structural variants. Single cell tracking shows that this mechanism is active throughout leukemic evolution with evidence of localized clustering and re-iterated deletions. Integration of point mutation and rearrangement data identifies ATF7IP and MGA as two new tumor suppressor genes in ALL. Thus, a remarkably parsimonious mutational process transforms ETV6-RUNX1 lymphoblasts, targeting the promoters, enhancers and first exons of genes that normally regulate B-cell differentiation.

Insertions and deletions target lineage-defining genes in human cancer
Marcin Imielinski (Cornell University)

The speaker examined some of the challenges and nuances involved in identifying and interpreting insertions and deletions in human cancer. Unlike outright mutations, in which (for example) an A in a gene is transformed to a C, insertions and deletions changes the actual length and shape of a genome. This makes it somewhat awkward to fit them into traditional phylogenetic analysis-tools. Yet these forms of mutation are common and important steps in the progression of a cancer. The speaker's thesis is that, in many identified cases, insertions and deletions are actually the mutations which characterize particular kinds of cancer-clones, which means that not only must these mutations be examined if we wish to infer cancer-lineages, but they must be targeted and coped with in their particular locations if we are to halt or prevent a cancer's spread. This was the main message, but the speaker also presented some of the methodology by which these conclusions were derived, which included feature association, a technique for inferring and grouping by the qualitative effects of such mutations.

WEDNESDAY SEPTEMBER 28, 2016

Circulating cell-free DNA for noninvasive tumour profiling
Dana Tsui (Memorial Sloan-Kettering Cancer Center)

Dr. Tsui started her talk by giving some background on her research subject. She used liquid biopsies to determine the outcome of treatments. She mentioned that for pregnant women, a blood test for Down's syndrome' gives better results. She said that we can use the same technique in cancer by investigating ctDNA levels in plasma of cancer patients. ctDNAs are detectable in different types of advanced cancers. The level of ctDNAs decreases after surgery. Dr. Tsui then said that we could use circulating cell-free DNA for identifying non-invasive cancers. She mentioned that EGFR was the first molecular detection method, which used blood instead of tumor.

Dr. Tsui mentioned that the interpretation of representations of tumor heterogeneity in plasma and other body fluids could improve clinical decisions. The speaker also mentioned that plasma exome can be used for cost-effective discovery of resistance mechanism. She also emphasized that whole genome analysis provides comprehensive overview of the cancer before and after the surgery. In plasma sample, they picked p53 and EGFR to capture metastasis.

She showed that circulating levels of somatic mutations correlates with mutations in the tumor, and ctDNA tracks differential treatment response across metastatic deposits. ctDNA can also identify potential drivers of treatment resistance.

Genetic and epigenetic determine leukemia evolution
Dan Landau (Cornell University)

Dr. Landau started his talk by saying that they study chronic leukemia because they can easily get time-course blood samples. He mentioned that CLL harbors marked clonal complexity, and about 50% mutations are found in sub-clonal. He added that sub-clonals come after clonals, and clonal diversity can be used to predict the outcome. He emphasized that increased heterogeneity prior to treatment results in faster disease relapse, and in many cases studying pretreatment clonal admixtures predicts the future evolutionary trajectory of relapsed disease.

In order to integrate epigenetic and genetic, he collected blood samples of patients and compared with normal B-cells. Then, he presented the results of higher intra-tumoral heterogeneity in CLL vs. Normal B cell samples. He used two potential models for methylation heterogeneity. He developed a method to measure locally disordered methylation, proportion discordant reads (PDR), and showed that stochastic disorder forms the basic cancer-related methylation changes. He presented some data revealing that there are some specific changes in the methylations in cancer samples compared to normal cells. Moreover, methylation disorder predicts intra-tumoral transcriptional heterogeneity. Dr. Landau showed that CLLs have uniformly elevated PDR compared to normal cells.

Deep and Shallow Perspectives on Tumour Evolution and Heterogeneity
David Wedge (University of Oxford)

Dr. Wedge presented, compared, and contrasted two possible approaches to studying the evolution of tumors. There is the “deep” approach, whereby we sample a very great number of cells from only a few tumors, and the “shallow” approach, whereby we examine single samples from a large number of tumors. These two approaches shed different kinds of light on the nature of cancer, in general and specifically, yet can be used in conjunction to attack the same problems. For example, to infer the evolutionary history of a single tumor, one must obviously take a large number of samples from it; however, viewing the evolutionary patterns of many different tumors can lead us to draw generalizations about trends in cancer progressions. The two methodologies thus complement and support each other, and both are valuable.

(Cancer) Genomics via (Sub) Optical Mapping
Bud Mishra (Courant Institute, New York University)

Dr. Mishra gave a survey of several probabilistic methods for fruitfully analyzing genomic cancer data. He phrased portions of the talk in a colloquial, almost philosophical vein, giving macro-world examples of the difficulty of inferring causation, or the importance of following the scientific method, before applying these principles to cancer. Specific issues touched upon included the relation of mutations to survival-time and methods for coping with high false positive rates in inferring mutations. He closed with his view of the ultimate goal of cancer genomics - to examine a patient's cells and fully chart the progress of the disease, and then infer the best methods of research from existing knowledge.

Scalable latent-factor models applied to single-cell RNA-seq data separate biological drivers from confounding effects

Florian Buettner (European Bioinformatics Institute)

Dr. Buettner spoke about statistical methods for coping with the imprecision of RNA-seq data. In particular, he introduced a method called scLVM (single-cell latent variable model) whose purpose is to differentiate collections of single cells, and identify the factors which truly distinguish them. As the name of the method suggests, one focus of the method is to give due account to variables that have not been observed, i.e. that are latent, and thereby avoid falling into the pitfall of equating one's dataset with the population itself. Though not specifically designed for cancer data, this method lends itself well to analysis of RNA-seq data taken from single cancer cells.

THURSDAY SEPTEMBER 29, 2016

Inference and validation of large-scale causal gene regulatory networks from transcriptomic data

Benjamin Haibe-Kains (Princess Margaret Cancer Research Centre)

Dr. Haibe-Kains discussed that multiple methods exist to infer undirected large-scale regulatory networks from collections of transcriptomic data. However very few network inference methods can infer the directionality of predicted gene interactions, despite this being key in the process of better interpreting GRNs. Another challenge when inferring large-scale GRNs consists in quantitatively assessing their validity. Popular, however weak, validation procedures include (i) simulation; (ii) using incomplete 'gold standard' datasets, such as known transcription factors and their targets, which only partially recapitulate the interactions that can be inferred from transcriptomic data; and (iii) using low-throughput laboratory experiments to validate a few predicted interactions, which represent only a very small and potentially biased part of the inferred GRN.

To address these issues, Dr. Haibe-Kains et. al have developed mRMRe, an ensemble approach for network and causality inference, and their integration of priors. They applied their new method on a large collection of approximately 500 shRNA experiments with gene expression profiles of cancer cell lines before and after knockdown of 3500 genes. This unique dataset allowed them to infer a regulatory network for 978 landmark genes in multiple cell types and determine the quality of the results quantitatively. The results suggest that the complexity of the underlying biology and noise in the experiments make it very challenging to infer meaningful gene-gene interactions. This study highlights the need for quantitatively assessing the predictive value of regulatory networks. It is important to note that large sample size does not necessarily yield high quality networks.

Complex analysis of proto-invasion dynamics

Caleb Bastian (Princeton University)

In cancer, certain dynamics of early invasion can significantly and persistently influence adjoining and downstream processes. Dr. Bastian studied early invasion dynamics using mathematical models and analysis tools from the complexity sciences and generated experimental hypotheses. In particular, he used Sobol systems, which are high dimensional model representations, to study how the inputs affect the outputs in a very complex biological system. He showed that such variance reduction techniques can mathematically determine which parameters are of importance

in the outcome of a system. For a given system with hysteresis, he tested hypotheses within in vitro and in vivo settings, concluding necessary empirical conditions for key dynamics.

Cancer progression and evasion under treatment

Ignaty Leshchiner (Broad Institute of Harvard and MIT)

Dr. Leshchiner presented some of the methods and difficulties involved in mapping the response of cancer to treatment. A central problem in this arena is determining which “clones” of the cancer, which are effectively different sub-species forming portions of the same tumor, are affected or even eradicated by treatment, which are not affected, and, if after treatment new treatment-resistant clones emerge, from which old clones these new clones are descended. One method for addressing such questions is PhylogicND, a computational technique looks at the abundances of cells which possess a specific somatic mutation, and thereby inferring the clonal makeup of the cancer. This method has enjoyed some success in assessing the effectiveness and shortcomings of a given treatment regime.

Inferring symmetric division parameters from phylogenetic tree and mesoscale population metrics of cancer stem cell-driven tumours in silico

Jacob Scott (Cleveland Clinic)

Dr. Scott spoke on the importance of symmetric stem-cell division rate as an informative trait of a cancer. The stem-cell division rate is typically recognized as the most important parameter in modeling the macroscopic behavior of a cancer - however, it is rather difficult to measure and also dynamic with time. The speaker therefore presented a scheme whereby the effects of a changing symmetric cell division rate could be observed by examining the size, shape, and evolutionary history of a tumor. The scheme was constructed on the basis of a cellular automaton model which simulated the progression of a cancer. A number of metrics, notably the normalized Sackin index, have proved under this scheme capable of distinguishing between tumors whose symmetric division rates are low or high.

Computational Cancer Immunogenomics

Elaine Mardis (Nationwide Children’s Hospital)

Dr. Mardis provided an introduction to the field of cancer immunogenomics and then described some of her own work in the field, which focused on vaccines. The underlying idea is that the mutations which “cause” a cancer are often the same from patient to patient, and therefore if we can prevent these mutations, we can prevent or at any rate substantially reduce the probability of cancer occurring. However, identifying these mutations, and also methods by which they can be guarded against, is a challenging task which requires some very specialized biological considerations. She then focused on the binding of peptides to HLA, and her use of RNAseq data, and more generally a computational approach, for identifying and stopping the mutations which trigger cancer genesis and spread.

Quantitative models of metabolism in health and cancer

Jason Locasale (Duke University)

Dr. Locasale introduced the idea of considering and modeling the metabolism of cancer, which is a topic whose importance is obvious, as a cancer which cannot metabolize will soon die out. The speaker focused on two nuances of cancer metabolism. The first was a phenomenon called the Warburg effect, whereby most cancer cells metabolize principally by glycolysis followed by lactic

acid fermentation, which is a different means of metabolism than that employed by most normal cells. This effect, though well-documented, is not well-understood, and Dr. Locasale described some possible methods for comprehending it. Secondly, he spoke about one carbon metabolism, which is a specialized form of metabolism for handling one-carbon groups, which are volatile. He then presented a network model for one carbon metabolism in cancer, and argued that certain variations in it are sufficient to characterize particular epigenetic marks in histones.

Cellular Immunome characterization in cancer patients using multiparametric flow cytometric analysis

Gerard Lozanski (The Ohio State University)

Dr. Lozanski presented some examinations of the cellular immunome's response to cancer, using novel multiparametric analysis. The phrase "cellular immunome" refers to the immune system's practice of keeping a watch over all cells to ensure that they are not behaving "selfishly" but are working for the good of the organism to which they belong - that is to say, that they are not behaving like cancer cells. The cellular immunome is actually a powerful and on the whole extremely effective safeguard in this respect, and it is informative to know how it breaks down and allows cancer to emerge. Dr. Lozanski's focus is on the method of "flow cytometry," which is a purely experimental technique involving lasers and mirrors. The goal of flow cytometry in this context is to examine the cancer cells' ability to "cloak" themselves, masquerading as well-behaved cells with which the Cellular Immunome need not be concerned.

FRIDAY SEPTEMBER 30, 2016

Combinatorial approaches for analyzing intra-tumor heterogeneity

Iman Hajirasouliha (Cornell University)

High-throughput sequencing of tumor samples has shown that most tumors exhibit extensive intra-tumor heterogeneity, with multiple subpopulations of tumor cells containing different somatic mutations. Recent studies have quantified this intra-tumor heterogeneity by clustering mutations into subpopulations according to the observed counts of DNA sequencing reads containing the variant allele. However, these clustering approaches do not consider that the population frequencies of different tumor subpopulations are correlated by their shared ancestry in the same population of cells.

As a result, Dr. Hajirasouliha introduced the binary tree partition (BTP), a novel combinatorial formulation of the problem of constructing the subpopulations of tumor cells from the variant allele frequencies of somatic mutations. He showed that finding a BTP is an NP-complete problem. Furthermore, he derived an approximation algorithm for an optimization version of the problem and presented a recursive algorithm to find a BTP with errors in the input. The resulting algorithm outperforms existing clustering approaches on simulated and real sequencing data.

Human papillomavirus integration in the pathogenesis of human cancers

David Symer (The Ohio State University)

Genomic instability is a hallmark of human cancers, including the 5% caused by human papillomavirus (HPV). Dr. Symer reported a striking association between HPV integration and adjacent host genomic structural variation in human cancer cell lines and primary tumors. Whole-

genome sequencing revealed HPV integrants flanking and bridging extensive host genomic amplifications and rearrangements, including deletions, inversions, and chromosomal translocations. Hence, Dr. Symer presented a model of “looping” by which HPV integrant-mediated DNA replication and recombination may result in viral–host DNA concatemers, frequently disrupting genes involved in oncogenesis and amplifying HPV oncogenes E6 and E7. His high-resolution results shed new light on a catastrophic process, distinct from chromothripsis and other mutational processes, by which HPV directly promotes genomic instability.

Chromothripsis and kataegis from telomere crisis
John Maciejowski (Rockefeller University)

Telomere crisis occurs during tumorigenesis when depletion of the telomere reserve leads to frequent telomere fusions. The resulting dicentric chromosomes have been proposed to drive genome instability. Dr. Maciejowski examined the fate of dicentric human chromosomes in telomere crisis. He observed that dicentric chromosomes invariably persisted through mitosis and developed into 50–200 μ m chromatin bridges connecting the daughter cells. Before their resolution at 3–20 hr after anaphase, the chromatin bridges induced nuclear envelope rupture in interphase, accumulated the cytoplasmic 3' nuclease TREX1, and developed RPA-coated single stranded (ss) DNA. CRISPR knockouts showed that TREX1 contributed to the generation of the ssDNA and the resolution of the chromatin bridges. Post-crisis clones showed chromothripsis and kataegis, presumably resulting from DNA repair and APOBEC editing of the fragmented chromatin bridge DNA. Dr. Maciejowski proposed that chromothripsis in human cancer may arise through TREX1-mediated fragmentation of dicentric chromosomes formed in telomere crisis.

Autumn Workshop 3 - Dynamical Systems and Data Analysis in Neuroscience: Bridging the Gap
(October 17-21, 2016)

Organizers: Casey Diekman (New Jersey Institute of Technology), Uri Eden (Boston University), Leslie Kay (University of Chicago), Mark Kramer (Boston University), Horacio Rotstein (New Jersey Institute of Technology)

Report by: Reginald McGee, Omar Saucedo, and Min Wang

Monday, OCTOBER 17, 2016

Neural oscillations in the rat olfactory bulb: relationships to neural firing properties
Leslie Kay (University of Chicago)

In the first talk, Dr. Kay discussed her work on using the oscillations to understand the high level of statistics on neuronal firing. She started by showing a diagram of olfactory bulb (OB) in neuron system, and then presented two classes of principal neurons and two types of OB oscillations -- gamma and beta oscillations. Gamma oscillations represent the activity of a local network within the OB, and beta oscillations represent engagement of a system-wide network. Dr. Kay further described gamma oscillations and explained how they are related to the mitral and tufted cell network firing patterns. She also investigated the coherence of gamma oscillations across the OB and found that the gamma band coherent oscillation on the surface of OB produces an amplitude

pattern associated with meaningful appearing on the first full sniff of the odor. Dr. Kay then went back to the topic of circuit and discussed the connection between mitral and tufted cells, respiration and gamma oscillations from previous literature. She also showed the recent work with her collaborators on studying fast and slow OB gamma and beta oscillations. That is, fast gamma favors the early and gamma the later odor sampling period and the relative contributions of these oscillations are consistent across tasks. Moreover, Dr. Kay talked about the relationship between the unit statistics and local field potentials (LFPs), and came up with some interesting questions that will be addressed in the future. Finally, she used a publicly available dataset to show that the initial sniffs may carry most of the objective sensory information, and therefore understanding cortical circuits, even at biophysical level, depends on careful use of multiple behavior contexts and stimuli.

Statistical neuronal models: an overview

Uri Eden and Mark Kramer (Boston University)

Dr. Eden and Dr. Kramer together reviewed various statistical models on analyses of features of a local field potential (LFP) dataset for a single trial. They began by visualizing the data where voltage/time is plotted. Time zero indicates when the rat pokes its nose into an odor port in the experiment. To examine whether a consistent evoked affect appears across trials, they computed the event-related potential (ERP). They also showed the spectrogram to examine whether consistent rhythms appear across trials, and made a rastergram for all trials to check the spikes from a single cell. To visualize the firing rate/time, the post-stimulus time histogram (PSTH) is calculated. Then they introduced the first statistical model – generalized linear model which captures the post-stimulus change in firing rate with a single predictor -- time. Due to the bad representation of the PSTH in this model, they updated it by adding higher order terms in time, and the assessment results show a better fit to the PSTH. They also evaluated the spike field coherence and occupancy normalized histogram to characterize the relationship between the spikes and LFP. Furthermore, they added another predictor -- phase to build the third model which can capture the change in firing rate with phase. A histogram of the inter-spike intervals (ISIs) is also made to illustrate the time intervals between spikes. They further computed the power spectrum of the spikes and displayed the spike spectrum plot to explain the rhythmic activity in the spike train. By incorporating a third predictor -- history, they built the fourth model to characterize the change in firing rate due to past spiking. Finally, they combined all of the predictors into one "complete" model, and compared the Kolmogorov-Smirnov goodness-of-fit plot for their second model and the complete model.

Dynamic (deterministic) neuronal models: an overview

Horacio Rotstein and Casey Diekman (New Jersey Institute of Technology)

Dr. Rotstein and Dr. Diekman started by introducing the basic neuronal dynamic behavior including post-inhibitory rebound and resonant behaviors. They then described some useful system tools, including bifurcation, excitability, etc., to help understand the underlying mechanisms in neuronal dynamics. The first dynamic neuronal model they talked about is the passive membrane equation or Nernst-Planck model which combines Ohm's law and Fick's first law. They then reported the second model -- equivalent circuit model with components including capacities, batteries and conductors or resistors. Moreover, a widely used type of model called integrate-and-fire (IF) model is described and the spike rate adaption models with additional currents are explained in the context of an IF neuron. They continued to introduce another one of the most important neuronal models – Hodgkin-Huxley (HH) type model which ideally incorporates three

major ionic currents by using pioneering experimental techniques. The basic structure and scheme of the voltage-gated ionic channels are also provided to explain the HH equations. After further assumptions and simplifications, the HH type model can be reduced to a two-dimensional model where phase-plane analysis can be performed to explain the properties including limit circles of the reduced model. Moreover, the Wilson-Cowan equation, which is one of the “population” network model and captures the dynamics of interaction between subpopulations of very simple excitatory and inhibitory neurons, is provided after incorporation of two key parameters – strengths of connectivity and input. They finally concluded by summarizing the various degrees of complexity in the single neuron models and the necessity of incorporating chemical and electrical synaptic currents, and possibly short-term synaptic plasticity in network dynamics. The possibility of extending single compartment model to multi-compartments model, population models and neural fields is also discussed.

Some Statistical Issues in Spike Train Analysis

Robert Kass (Carnegie-Mellon University)

Dr. Kass focused on the standard framework for statistical analysis of spike train data, based on point process regression using the modern methodology of generalized linear models (GLMs). He suggested that spike train data is closely related to the leaky integrate and fire conception which he gave an example of oriented bar of light-firing V1 neuron of directional tuning. When examining this type of data, he presented a big statistical issue of how to grapple with the complexity while trying to assess the reliability and relevance of the results. One solution is to identify the network based on spike count correlations; however, harder problems that involve large dynamic networks often with covariates and latent variables are more difficult to deal with. One way to handle this statistical issue is to take a look at the problem in a Bayesian approach since this way of thinking gives an interpretable inference to relatively simple models, and the false discoveries can be controlled via Bayes’ Theorem. He promoted that identification of neural graph structure is a huge problem which can be solved by incorporating auxiliary information. Dr. Kass ended by advocating the replication of studies to validate experiments.

Tuesday, OCTOBER 18, 2016

Completing biophysical models of nervous systems

Henry Abarbanel (University of California, San Diego)

In this talk, Dr. Abarbanel presented the ideas and applications of the data assimilation tools to experimental data for determining the unobserved neuron state variables and the unknown parameters given the biophysical Hodgkin-Huxley (HH) model. He first gave the notations of various variables and explained how the state variables are connected via the model. Then an assumption of the conditional probability for path of system state variables conditioned on observed variables is provided to derive the conditional expectation of a function on the path which essentially formulates the inverse problem of inferring states and parameters into an optimization problem. Dr. Abarbanel further described two approaches, Laplace’s method and Monte Carlo search algorithm, to evaluate the high dimensional integrals involved in the computation of the conditional expectation. He employed the Laplace’s method and expanded the objective function around stationary paths. This shifts the numerical difficulty of the problem into the one of finding the lowest minimal of the cost function A_0 . He then proposed the annealing method to manipulate this cost function by varying the values within A_0 . To build confidence in the ability of his algorithm to return the correct values of parameters and states, he attempted twin experiments in

which he had enough knowledge and control of the system and experimental data. Another advantage of his method is that it contains ability to estimate corrections to first estimate. Dr. Abarbanel validated the model with results of data assimilation on voltage recordings of HVC neurons in vitro, showing that it exhibits key qualitative features and biophysical mechanisms found in other work. Finally, he showed results of applying the data assimilation procedure on synthetic and real voltage recordings of single HVC neurons.

Building bridges between model and experiment to obtain an essence of theta rhythm generation
Frances Skinner (Krembil Research Institute)

Oscillatory activities are hallmarks of brain output that are linked to normal and pathological functioning. But the cellular mechanisms underlying the oscillatory generation in the hippocampus are unclear. Dr. Skinner began by outlining the work on developing a novel cellular-based model to determine the mechanisms for how brain oscillations are generated. She then quoted the critical findings on theta rhythm generation and various sources of the causes which intuitively drive her current investigation. Dr. Skinner continued to introduce the background of population activities in rodent hippocampus. She took the discovery of theta oscillations (3-12 Hz) almost 80 years ago as an example to illustrate that multi-scale, nonlinear nature of our brains make the mechanism highly challenging to understand. Furthermore, Dr. Skinner described the previous work of parvalbumin-positive (PV+) interneuron network model with their limits and constraints. To address the difficulties in previous literature, she created network models that are tied to experimental work at both cellular and network levels to explore how the interneuron interactions affect the power of local oscillations. Her network models are composed of three different types of interneurons. They also include a spatially extended pyramidal (PYR) cell model to allow for a simple local field potential representation, and experimentally-constrained, theta frequency synaptic inputs to the interneurons as well. Moreover, by using theoretical insights and biological constraints, the models she developed can produce theta rhythms, thus suggesting the underlying essence of their generation. Overall, her network models reveal a dynamic interplay between different classes of interneurons in influencing theta power.

Fragility in the human decision making system: when internal biases hijacks logic
Sridevi Sarma (Johns Hopkins University)

Dr. Sarma began by stating the central role of decision-making in human personality and ability to learn and adapt. She then illustrated the dependent relationship between logic and emotion in decision making, and demonstrated that the rationality in logical decision makings is influenced by the internal biases including emotions. To understand the function of relevant neural circuits and the changes underlying disruption associated with age or psychiatric diseases in humans, she localized neural populations, circuits, and their temporal patterns on a millisecond scale and conducted an experimental study of gambling. In this experiment, twelve human subjects, implanted with multiple depth electrodes for clinical purposes, performed a gambling task while her collaborators and her recorded local field potential neural activity from deep and peripheral brain structures. She then proposed a closed-loop dynamical system model to explain the individual variability in decision making. The relationship between logical input and internal state is conceptually described, and the estimation algorithm and model results are presented. Furthermore, Dr. Sarma identified neural correlates of model variables. Her models suggest a spectrum of decision-makers that range from irrationally to logical, and analyses of the neural data suggest that, specific oscillations in brain structures, including anterior insula, amygdala and cingulate cortex are shown to influence betting behavior in a profound way. Moreover, Dr. Sarma

measured spike train observations from an epileptic network and applied a feedback controller. She then used a stochastic model of a neuronal network to simulate both seizure and non-seizure activity, and found that the epileptic cortex is fragile in the sense that seizures manifest through small perturbations in the synaptic connections that render the entire cortical network unstable. Finally, she concluded that these findings provide new insight into how humans link their internal biases to decisions.

Sequences of attractor-like states and the prediction of consumption behavior in single trials

Don Katz (Brandeis University)

Dr. Katz started his talk by showing several interesting examples of consumption decision making on animal's determination of ejecting or consuming an already identified stimulus in the mouth. He then explained that rodent cortical single-neuron taste responses come to predict such consumption decisions across the preceding the consumption or rejection itself, and decision-related firing emerges after stimulus identification. He further conducted a hypothesis that decision making in gustatory cortex (GC) is well described as occurring in a sudden transition with trial-specific timing rather than following a substantial ramp. To test it, Dr. Katz analysed single-trial ensemble activity using hidden Markov models, and showed these decision-related cortical responses to be part of a reliable sequence of states separated by brief state-to-state transitions, the latencies of which vary widely between trials. He also aligned data to the onset of the state that dominates during the time period in which single-neuron firing is correlated to taste palatability, and showed that the apparent ramp in stimulus aligned choice-related firing is a much more precipitous coherent jump. This jump in choice-related firing resembled a step function more than it did the output of a standard ramping decision-making model, and provided a robust prediction of latency in single trials. Together, these results including the data reveal a dynamical characterization of the taste system in action and demonstrate that activity related to naturalist consumption decisions emerges instantaneously in cortical ensembles.

Inferring synaptic conductances from spikes using a biophysically inspired extension of the Poisson generalized linear model

Jonathan Pillow (University of Texas)

Dr. Pillow began his talk with a review of generalized linear models (GLMs) and explaining his group's interest in a tradeoff between making the models easy to fit, simulate, and analyze and still being able to have dynamical flexibility. The speaker's work was motivated by the question of whether a synaptic conductance-based model can correspond to a GLM. Despite the limited mechanistic insights when using GLMs for neural data, an advantage to this approach was that for suitable choice of a nonlinear filter log-likelihood for the parameter space was always concave and this guaranteed fast optimization and location of maxima for the log-likelihood. This fact presented a parameter fitting approach for the derived conductance-based point-process model where initial values of the conductance parameters are found by fitting the GLM parameters. This approach is favorable due to fewer constraints on the parameter space for the conductance-based point process model. After fitting the conductance-based point process model to experimentally collected conductance and spike-train data, the model was able to outperform the GLM in spike prediction.

Model-based Observation and Control for the Brain: From Control of Seizures and Migraines, to Reducing Infant Brain Infections in Africa

Steven Schiff (Penn State)

Dr. Schiff started by motivating the need for model-based observation and control in neuroscience.

He then sought to use nonlinear control theory to understand both single cell and neural network dynamics with specific applications in Parkinson's disease, seizures, and spreading depression. The key idea here is to control how the brain moves between steady state whilst avoiding areas of parameter space where seizures and depression occur. The key mathematical tool in this work was the Kalman filter and Dr. Schiff gave a review of nonlinear ensemble Kalman filtering and discussed how they would be used in conjunction with Hodgkin-Huxley style models. The models considered had been expanded to include intra- and extracellular states to respect conservation laws. Moreover, oxygen dynamics were added to connect flux through the glial sheath and ion pumps to the state variables. These additions allowed Dr. Schiff to track the changes in volume changes in the cell depending on osmotic pressure differences. For computational tractability a reduced model was considered and cell volume was used as a bifurcation parameter to find oscillatory regions and led to an explanation of physiological ceilings. Finally, the speaker found that normal forms revealed degenerate Hopf bifurcations in the reduced models.

Spike-free Inference from Calcium Imaging

Kyle Lepage (Allen Institute for Brain Science)

Dr. Lepage began his talk with a review of a mouse dataset collected for the past four years. The objective of this work was to achieve temporal-kernel estimation to predict spikes from calcium imaging. A key component of this work was a generative model of fluorescence, created with dynamical systems. The key problem considered was determining the rate of an inhomogeneous Poisson process by through inference of kernel parameters related to spike timing and fluorescence. The speaker assumed that experimental covariates were related to the inhomogeneous spike rate by a multiplicative factor β and three approaches (regression, variational Expectation Maximization, and approximate Maximum a posteriori estimation) to estimating this factor were discussed. The speaker plans to continue this work by further characterizing the relationship between calibration data and the collected data and also refine spike-detection and inference algorithms.

Wednesday, OCTOBER 19, 2016

Inferring Dynamics of Neurons from Field Potentials in the Auditory Brainstem

Joshua Goldwyn (Ohio State University)

In this talk, Dr. Goldwyn started by defining membrane potential and its relationship between intracellular voltage and extracellular voltage. The ongoing activity of neurons generates a spatially and time-varying field of extracellular voltage. He stated that this extracellular voltage field reflects population-level neural activity, and what concern with whether it modulate neural dynamics and the function of neural circuits. To tackle this question, he provided a cable theory framework to study how a bundle of model neurons generates extracellular voltage and how it feeds back and influences membrane potential. He found that these ephaptic interactions are small but not negligible, and the model neural population can generate extracellular voltage with millivolt-scale amplitude. After using passive cable theory to systematically study ephaptic coupling, he presented a test case: the medial superior olive (MSO) in the auditory brain stem. He found that pharmacological agents could be used to block inhibition and/or excitation in future experiments. Finally, he stated that parsimonious models explain frequency-dependent patterns of extracellular voltage in vivo in response to range of tone frequencies.

Temporal Patterns of Intermittent Neural Synchronization

Leonid Rubchinsky (Purdue University)

Dr. Rubchinsky presented his work on intermittent neural synchronization. He described it as the activity in the brain which is involved in a variety of brain functions including perception, cognition, memory, and motor behavior. Excessively strong, weak, or otherwise improperly organized patterns of synchronous oscillatory activity appear to contribute to the generation of symptoms of different neurological and psychiatric diseases. However, neuronal synchrony is frequently not perfect, but rather exhibits intermittent dynamics. So the same synchrony strength may be achieved with markedly different temporal patterns of activity. He discussed this situation from two perspectives: the phase-space perspective and associated considerations of dynamical systems theory and time-series analysis perspective. He then applied this analysis to the neurophysiological data in healthy brain, Parkinson's disease, and in drug addiction disorders. He found that the intermittent synchrony may be a result of a propensity of the brain to be engaged in the brief synchronized episodes of activity needed for movement control. Parkinsonian state may result in departure from very transient dynamics to moderately transient dynamics. He summarized his talk by stating that neural synchrony has a very specific temporal pattern, and changes in patterns of synchrony may proceed changes in its strength.

Challenges in Parameter Estimation for Conductance-Based Models**Peter Thomas (Case Western Reserve University)**

Dr. Thomas began presentation by stating his goal for the project which is to understand the relationship between channel noise randomly gated ion channels and interspike interval variability. Stochastic effects, arising from these random gating of ion channels, complicate efforts to estimate conductance based model parameters, such as channel conductances and kinetics, from electrophysiological data. Channel noise is not always harmful; however, some parameters that are not identifiable in a deterministic model can be estimated within a stochastic model. For example, channel noise may facilitate estimation of the numbers of channels in a given cell. On the other hand, unlike their deterministic idealizations, neurons with stochastic conductances do not produce periodic orbits, thus presenting a moving target for trajectory-based parameter estimation. He gives a two-stage optimization approach in which given a set of fixed inner parameters and recorded voltage trace, the simulation optimize the outer parameters. After that you apply your favorite search routine to the inner parameters, and repeat, minimizing mean square predicted current error. He concludes by discussing the related challenges in estimating parameters of conductance-based models in the presence of channel noise.

Neuronal Responses to Stimulus Pairs in Visual Cortex**Susanne Ditlevsen (University of Copenhagen)**

In this talk, Dr. Ditlevsen started by asking how does the brain process visual information when more than one object is presented. She proceeded by attempting to answer this question through statistical analyses of responses from single cells to pairwise presented objects. It is a statistically challenging problem how to infer such behavior and distinguish between different explanatory models from neurobiological data. Particular challenges are that data are partially observed, highly noisy and autocorrelated. A standard way to deal with noisy data is to average over trials. She argued that this might blur or entirely remove essential characteristics and mechanisms, which are fundamental for understanding brain function. She proposed two opposing models which are serial processing and parallel processing. Both models were used to compare the abilities to account for spike trains recorded. In the response-averaging model, the firing rate of the cell to a pair of

stimulus objects is a weighted average of the firing rates to the individual objects. By contrast, in the probability-mixing model, the cell responds to the pair of objects as if only one of the objects was present in any given trial. Here we compare the abilities of the two models to account for spike trains recorded from single cells in the middle temporal visual area (MT) of rhesus monkeys, using point process techniques. She concluded that the results supported the probability-mixing model.

Inference of connectivity from extracellular data

Asohan Amarasingham (City College of New York)

In this talk, Dr. Amarasingham addressed the question of understanding how properties of synaptic connectivity vary across behavior by approaching it indirectly from the perspective of biophysical models. He first interpreted the definition of trial-to-trial variability in stochastic models and explained its decomposition by providing several well-known examples, including the spike count variability and the spike timing variability. Then he described the doubly stochastic spiking models and summarized that their setup is ill-posed because of the issues and constraints on timescale caused by different forms of trial-to-trial variability. To deal with such concerns, Dr. Amarasingham focused on a resampling approach called jitter to produce statistically correct hypothesis tests in terms of the conditional distribution on the locations of spikes or spike patterns. He reviewed the jitter techniques, illustrated by both simulation experiments and selected analyses of spike data from motor cortical neurons. He replied on intuitive and rigorous statistical framework known as conditional modeling to reveal otherwise hidden assumptions and to support precise conclusions. He also reviewed the exact tests for the significance of repeated fine-temporal patterns of spikes. Furthermore, Dr. Amarasingham worked with simple models of monosynaptic transmission and varieties of background noise, and sought conditions for precise pre- and post-synaptic spike time relationships. He demonstrated that, in addition to connectivity parameters, low variability of subthreshold potentials appears to be an important ingredient. He discussed the plausibility of this hypothesis, and its implications for measuring input variability experimentally as well as for nonparametric statistical inference of connectivity from extracellular data from the conditional modeling perspective.

A model of plasticity-dependent activity in rodent hippocampus during spatial exploration

Alex Roxin (Centre de Recerca Matemàtica)

In this talk, Dr. Roxin studied how spike-timing dependent plasticity (STDP) during spatial exploration shapes the patterns of synaptic connectivity in model networks of place cells in rodent hippocampus. He began by introducing two types of attractors in memory models and reviewing the previous work of rodent place cell activity during spatial exploration. He then presented a simple firing rate model and showed how an STDP rule can lead to the formation of attracting manifolds, essentially patterns of activity which represent the spatial environment learned. He explained that these states become spontaneously active when the animal is quiescent, reproducing the phenomenology of replays. Moreover, he found that the attractors are formed most rapidly when place cell activity is modulated by an ongoing oscillation. And the optimal oscillation frequency can be calculated analytically, which is directly related to the STDP rule, and for experimentally determined values of the STDP window in rodent slices gives values in the theta range. Furthermore, Dr. Roxin demonstrated that a major prediction of these models is that the structure of replay during sharp-wave/ripples should undergo a transition during exploration. Specifically, at a critical time the sequential correlation (SC) of replay with trajectories in the currently explored environment should increase. He also looked for this increase by examining the activity of hundreds of simultaneously recorded hippocampal cells in rats exploring a novel

environment from the laboratory of Eva Pastalkova. Finally, Dr. Roxin concluded that the model of spatial exploration predicts the increase in SC of hippocampal activity, and the increase in SC depends on theta-modulation and the most effective frequencies depend on STDP window.

THURSDAY, OCTOBER 20, 2016

Emergent dynamics from network connectivity: a minimal model

Carina Curto (Pennsylvania State University)

Dr. Curto began her talk with an overview of how memory states can be identified with fixed point attractors of a neural network. Classically, Hopfield Networks have been used to model memory patterns due to symmetry results that guarantee the existence of fixed point attractors. The speaker gave an example regarding place cells to motivate how activity they and other neural cells exhibit might better be studied with periodic attractors due to intrinsically observed sequences and rhythms. The key question in this work is how does the connectivity of a network shape emergent dynamics? To study connectivity, threshold-linear models were used and ultimately relaxed to a case specified entirely by the edges present in the graph, called Combinatorial Threshold-Linear models. Results for these models were presented that characterize the possible dynamics; limit cycles, chaos, and quasi-periodic behavior were all observed for different adjacency matrices.

Adaptive algorithms for biomarker suppression with deep brain stimulation

Tay Netoff (University of Minnesota)

Dr. Netoff discussed the mathematics behind recent technological advances in using deep brain stimulation to help relieve tremors and seizures in patients with Parkinson's disease and epilepsy, respectively. Both model-based and model-free approaches were considered to optimize phasic stimulation for Parkinson's treatment and to optimize stimulation frequency for epilepsy treatment. In the first section of the talk, the speaker used phase response curves from their model to select the optimal phase. For the model-free approach, a reinforcement learning algorithm identified the area in state space to apply the stimulus in an unsupervised manner. In the second half of the talk, Dr. Netoff largely considered a seizure model. The first result here was that nullclines could be used to determine the minimum stimulation energy to suppress seizures. The reinforcement learning algorithm was also used in combination with the seizure model and a closed loop linear quadratic control to predict stimulations that lead to the persistence of seizure suppression.

Fernando Fernandez (Boston University) [In place of Sara Solla]

Dr. Fernandez focused on understanding mechanistic factors behind the high variability in the timing of spike trains and how it correlates with variability in voltage. The speaker was interested in cases when anesthesia is and isn't applied and motivated this study with a review of published data on voltage and membrane dynamics. A network mechanism key to this framework is that of balanced activity, which encompasses both feed-back and feed-forward inhibition. Balanced activity is the mechanism necessary for generate variable voltage and spike discharge. Experimentation showed that the timescale of spontaneous fluctuations was inconsistent with balanced activity. To resolve this finding, the speaker used an Ornstein-Uhlenbeck process for both excitation and inhibition dynamics to create a single cell model. The resulting model allowed the speaker to understand how holding voltage impacted fluctuations. A key finding was that balanced synaptic activity in a single compartment generated a nonmonotonic relationship between the size of voltage and fluctuations and mean holding voltage.

Inferring Synaptic Plasticity Rules From the Statistics of Neuronal Responses to Sets of Novel and Familiar Stimuli

Nicolas Brunel (University of Chicago)

Dr. Brunel spoke on mechanisms of learning and memory in cortical circuits. The speaker sought to understand the relationship between plasticity rules and the statistics of responses when applying different stimuli to a model. The key mathematical tool in this work were coupled firing rate model comprised of states for excitatory and inhibitory cells. Novel and familiar stimuli were applied and the distributions of firing rates were used to infer learning rules and ultimately a transfer function was constructed from the distributions arising from the novel stimuli. The speaker demonstrated that when using the rule derived from the in vivo dataset in a network model that the learning dynamics were stable. Moreover, this derived rule improved representation of the output stimuli.

Attractor dynamics in the head-direction system

Adrien Peyrache (McGill University)

The speaker began his talk with an overview of how the brain receives, processes, and retains sensory inputs. The aim of the work Dr. Peyrache presented was to understand whether the head direction system is sensory driven or internally organized. The speaker hypothesizes that the head direction system is an attractor network, in particular, a ring attractor. One of the first experimental results was that the timescale for the coordination of head direction depended on whether a brain was awake, in a slow wave sleep, or in REM sleep. When considering how synchrony plays a role in information transmission, experiments eluded to the head direction system being feed forward. The final portion of the talk was concerned with the question of how head direction systems are transformed into spatial code. Considering place fields instead of polar plots, the speaker found that animals use boundaries in combination with head direction signal to limit the number of directions they need to consider when exploring a space.

Diversity of Evoked Astrocyte Calcium Responses: Mathematical Modeling

Alla Borisjuk (University of Utah)

According to Dr. Borisjuk, evidence suggests that astrocytes play a key role in neuronal function through their calcium signaling. She presented a mathematical model of astrocyte calcium signaling that provides a tool to study the underlying mechanisms of these signals. Using experimental data from her collaborator's lab and model simulations, she categorize astrocyte calcium responses, evoked by focal, brief (<250 ms) ATP applications, into four types: Single-Peak, Multi-Peak, Plateau, and Long-Lasting responses. Applying this categorization, she discovered experimentally that as we move from the soma to the large and, finally, small processes, the occurrence of Single-Peak responses decreases, while the occurrence of Multi-Peak responses increases. They used their model to provide insight into the possible sources of calcium response variability: (1) temporal dynamics of IP₃, and (2) relative flux rates through calcium channels and pumps such as store-operated calcium (SOC) channels, SERCA pump. Further, their model generates predictions about the effects of blocking calcium channels/pumps; for instance, blocking SOC channels is expected to eliminate Plateau and Long-Lasting responses. Relative sizes of calcium currents can be predicted based on response distributions catalog.

FRIDAY, OCTOBER 21, 2016

Improved Signalling as a Result of Randomness in Synaptic Vesicle Release

Calvin Zhang (University of Arizona)

Dr. Zhang introduced some basic properties of synaptic transmission. Unlike the all or none potentials, synaptic transmission is graded. It is therefore a favorite of hormonal pharmacologic and neural regulation of nervous activity. Vesicle fusion and the subsequent release of neurotransmitters is stochastic and its likelihood of occurrence is a crucial factor in the regulation of signal propagation in neuronal networks. The reliability of neurotransmitter release can be highly variable. Noise is not only a source of disturbance, but it also can be beneficial for neuronal information processing. The release of neurotransmitter vesicles in synapses is an unreliable process, especially in the central nervous system. Dr. Zhang showed that the probabilistic nature of neurotransmitter release directly influences the functional role of a synapse, and that a small probability of release per docked vesicle helps reduce the error in the reconstruction of desired signals from the time series of vesicle release events. He gives the expected rate of vesicle release equation which shows that during any time interval in which the spike density is constant, the expected rate of vesicle release approaches the mean rate of vesicle docking. He summarized that the stochastic vesicle release process provides a synaptic mechanism through which the Weber-Fechner principle in the sensory system can be realized.

Mesoscale Structures in Functional Neuronal Networks

Mason Porter (University of California Los Angeles)

In this talk, Dr. Porter established the relationship between micro, macro, and meso. Microscale structures deal with information centered on nodes, edges, or other structures. Macroscale structure regard the properties of microscale properties across all nodes while mesoscale structures are middle-scale properties. The purpose of these definitions was to use a modularity quality function and assign nodes to communities to maximize the quality function. To find an appropriate null model, he treated each layer as a network with a specified spatial resolution of interest, and had both intra-layer edges and inter-layer edges. He noted that multilayer community detection doesn't care whether the time series come from experimental measurements or output from dynamical systems. Leverage knowledge of well-known dynamical systems to help with methodological development validation, explore ideas, and perhaps obtain insights on the dynamical systems themselves. Dr. Porter gave an example where dynamic reconfiguration of human brain networks during learning process. From his study, he saw flexibility of nodes predicts simple motor learning, and there was good correspondence between structure and dynamics for flexible nodes in network periphery and stiff nodes in network core.

Explanation of Variability in Data through Optimal Transport

Esteban Tabak (New York University)

Dr. Tabak began his talk by providing an example of different types of data, and explained that every data rich field has similar explanatory variables which enrich and confound the variability in the quantities of interest. He stated that the individualized nature of data can be both a blessing (personalized medicine, micro-local weather forecast more generally detailed models with high predictability) and a curse (confounding factors challenge statistical analysis). There are four complementary tasks that help with this procedure which are explaining variability due to known factors, filtering attributable variability, uncovering previously unknown variability factors, and making individualized predictions. Generalizations of optimal transport provide the right language and tools for these four task. Dr. Tabak proceeded by explaining the methodology based on the

theory of optimal transport that he developed to attribute variability in data sets to known and unknown factors and to remove such attributable components of the variability from the data. Among all maps and target distributions that achieve this goal, the procedure selects the one that minimally distorts the original data. He went on to discuss the relevance of this methodology to medicine and biology, including the amalgamation of data sets and removal of batch effects, the analysis of time series, the analysis of dependence among variables and the discovery of previously unknown variability factors. Dr. Tabak ended his talk by stating that many classical tools can be viewed as particularly simple instances of this methodology which allows one to generalize them broadly.

Autumn Workshop 4: Population Models in the 21st Century **(November 14-18, 2016)**

Organizers: Marisa Eisenberg (University of Michigan), Mark Lewis (University of Alberta), Lauren Meyers (University of Texas)

Report by: Punit Gandhi, Farrah Sadre-Marandi, Omar Saucedo

MONDAY, November 14, 2016

Robust fitting of state-space models for reliable fish stock assessment

William Aeberhard (Dalhousie University)

State space models (SSM) are important for fisheries science because it allows for sustainable management for fisheries which relies on the output of fish stock assessment. These types of models represent a large framework for accounting measurement error and unobserved random variables. Trying to estimate parameters by fixing them is known to be highly sensitive to the correct specification of the model. Thus, a more robust fitting procedure is required.

The goal of Dr. Aeberhard's talk was to develop robust SSM methodologies for models that allow for both errors and misspecifications in the measurement equation and in the state equations. There is also a need to limit impact of deviations from model assumptions on estimations, inference, and predictions. A typical example is fish stock population dynamics which usually consist of noisy data that includes outlying observations and deviations from both the state and measurement equations. The type of robustness can be called "distributional" robustness because the model is thought essentially as a distributions assumed for the data. Therefore, the goal is to compute meaningful quantities related to the assumed distribution model which is ongoing work.

Dealing with management

Alan Hastings (University of California, Davis)

One of the goals of population models as the field matures is to use them in making management decisions. Dr. Hastings discussed different approaches for developing population models for management, and emphasized both general issues of dealing with uncertainty, and also considered specific systems including an invasive plant species. Dr. Hastings began by pointing out that society is facing a growing number of environmental issues and we may not realize a given problem until it is too late. Moreover the issues can be difficult to manage, particularly when they appear on a global scale. Decisions about management rely on predictions, and thus it is important to understand the associated uncertainties along with time scale over which a prediction is valid as well as the response time of the system.

As a general framework Dr. Hastings proposed to first use results from simulations of an explicitly spatial model to develop a simplified model of time evolution. Then analyze control of a linearized version of the simple model using linear programming in order to optimize a management strategy. He discussed an invasive plant species on the Northwest United States as an example. Management in this case was complicated by the fact that an endangered bird species used the invasive species as a habitat. The optimal strategy based on his analysis involved different management approaches at different times.

Assessing Species' Risk under Climate Change

Noelle Beckman (SESYNC, University of Maryland)

Global change affects the ecology and evolution of dispersal, limiting the ability of species to move or adapt to global change events. Due to the long-term and spatially-complex dynamics of plant populations, being able to understand and predict their responses to global change is empirically and mathematically challenging. By 2020, the extinction of known threatened species has been prevented and their conservation status, particularly of those most in decline, has been improved and sustained. Also, knowledge, the science base and technologies relating to biodiversity, its values, functioning, status and trends, and the consequences of its losses are improved widely shared and applied.

Using a Bayesian approach, one can synthesize existing data on dispersal, functional traits, and demography to generate virtual species with realistic dispersal kernels and life-history strategies. These virtual species are used to parameterize integrodifference equations and approximate population spread in continuous landscapes. Using this approach, predictors of risk are obtained which are related to easily measurable functional traits that will inform the types of species least likely to track a shifting climate. This research will help identify species at greatest risk and aid the development of conservation strategies to ensure their persistence under global change

Modeling for the Data You Have

Rebecca Garabed (The Ohio State University)

Interdisciplinary work is a vital part of mathematical biology. Dr. Garabed chronicled three stores of interdisciplinary collaborations that she participated in. Endemic food and mouth disease in Cameroon, environmental demographics and diarrhea in households, and amyloidosis in captive cheetahs were the three case studies presented. In the first study, they found estimates derived by modeling fitting for the time-varying force of infection. Some of the conclusions from their case study was that they felt like they were not progressing; however, they built great foundations. Most of their progress came about when the modeler got hands on data which enabled them to obtain useful results.

The second case study started the foundation for more complex models. While they felt that they were going in circles, the conversation was useful to have because it helped them think about the fundamentals of the disease. In the third study case, they constructed a model for amyloidosis and fitted it to the confirmed cases. From their first analysis, they had to re-think the model due to the highly heterogeneous system and the skewed results being obtained. Three question they needed to answer: Are all mechanisms reasonable?, Which live cheetahs should they target for necropsy upon death?, and Which dead cheetahs' samples should we track down to differentiate mechanisms? Some of the lessons learned was that interdisciplinary work is iterative rather than linear. Though frustrating, interdisciplinary collaborations is worth the effort.

Forest Fire Risks: Assessing Historical Trends, Insurance Risks and Health Effects
Charmaine Dean (University of Western Ontario)

Fires are a significant natural disturbance in forested ecosystems. In 2015, there was approximately 68,000 wildfires which burned an area about 20 mil acres. Lightning fires burns about 400 acres on average which is 9 times that of human-caused fires. Assessing trends forest fire risk is of significant concern to fire managers as well as for the insurance and health sectors because of impacts of such risks in these areas. In particular, determining trends in forest fire ignition risk as measured by increasing annual trends in ignitions, or the lengthening of the fire season within each year, or both of these factors, requires urgent attention. For example the 2016 Fort McMurray wildfire. It was discovered on May 1 and it burned approximately 590,000 acres. 90,000 people were evacuated and \$3.58 billion in insurance claims were filed. Climate change has been a factor in the rise of wildfires. Increasing temperatures could increase the number of ignitions and extend fire seasons. Studies using forecasts from climate models have suggested increased severity ratings, area burned, and ignitions. Some of the issues with climate impact studies is the origin and quality of historical data which can be a challenge when looking for climate change signals. The common problems are that the data is from different sources and there usually several changing measurement methods. However, satellite imagery has been a great tool to assist in determining the health risks related to forest fire smoke exposure.

TUESDAY, November 15, 2016:

Managing multiple sources of uncertainty: optimal outbreak response for Foot-and-Mouth Disease

Matthew Ferrari (Pennsylvania State University)

Decision-makers are often faced with a fundamental trade-off between the learning that will accrue through continued observation of a disease process and the opportunity cost of inaction. Structured decision-making and management seek to minimize opportunity cost of inaction, though the goals of the managers are not always clearly stated in terms that can be represented in models. These unstated goals can lead to conflict in objectives of multiple stakeholders. Models can be used to explore trade-offs among objectives and help to develop optimization scheme or policies. Though it is important to understand the uncertainty of models and parameters as well as the context.

If the optimal interventions are model specifics, then interventions should adapt to the changing state of knowledge rather than rely only on past epidemic data. To define an adaptive policy that responds to the changing state of information, the parameter estimates should be constantly updated with current data during the outbreak. Forward simulations can be run of all possible controls conditional on parameter estimates at week one and compared to forward simulations of all possible controls conditional on final week T. As information accrues, the projections will change, and set of possible outcomes change though eventually converging as the data stabilizes over time. This emphasizes that the “best” action is unlikely to be the same for all possible realizations, leading to a state-dependent adaptive policy that can result in significant gains over conventional static management.

Connecting Models with Data: Identifiability and Parameter Estimation of Multiple Transmission Pathways

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. For the case of a Cholera SIWR model, it is shown that more transmission pathways yield more unidentifiability issues. Specifically transmission pathways are often unidentifiable, but water and rainfall data can improve estimates. These results highlight the importance of incorporating environmental data when examining a waterborne disease.

Modeling selection bias to enable accurate estimation and prediction**Gabriela Gomes (Liverpool School of Tropical Medicine)**

Specific study designs are proposed to overcome selection bias in infectious disease modeling and trial analysis. To prevent errors in translation, estimation of risk variance from randomized controlled trials should use a model that is compatible with that adopted for impact projections. Building frameworks that use estimates of protection from the lab to project bridges this gap in the field.

Using these frameworks on the Wolbochia bacteria, the preliminary data suggest three things. First, Wolbochia may increase variance in susceptibility to viruses, more consistently then it reduces mean susceptibility. Second, experimental designs with narrow conditions may unfairly appear irreproducible. There may be a case for more flexible experimental designs and analysis. Last, similar issues may arise in the assessment of stimuli in other infections, or in the quantification of cells that respond to a stimulus.

Modelling-assisted disease surveillance**Julien Arino (University of Manitoba)**

Suppose an infectious agent is introduced naturally or artificially somewhere on earth. Can we (1) provide information about the capacity of the Global Air Transportation Network (GATN) to facilitate the global spread of this infectious agent and (2) provide public health authorities with an evaluation of the risk they run of importing this agent into their system? These questions have been partially addressed by the Internet (trawling) surveillance, which uses automatic processing of internet sources (news, blogs, twitter, etc.) to monitor and provide early warning about the emergence or re-emergence of diseases. Yet these systems generate a lot of noise, situations awareness issues, and information overload.

This talk discusses ongoing work which uses the knowledge of the GATN to rank alerts generated by the internet trawling surveillance. An integrated platform of this kind helps to filter the large number of alerts generated by these systems, identify infectious disease threats at the earliest stages possible, and provide insights into which diseases are most likely to spread.

Model-Guided Design of Experiments and Data Collection**Alun Lloyd (North Carolina State University)**

The impact of model parameters on model outputs can be assessed using techniques from uncertainty quantification. We care about uncertainty because we need to understand limitations of our predictions or the biological conclusions that we draw from a model, and it helps better comprehend which components of the model do or do not contribute in an important way to its dynamics. Uncertainty gives a guide to data collection that would improve the modeler's ability to make predictions or to estimate parameters of interest. When it comes to modeling, uncertainty can be intrinsic stochasticity, or it may lay in the model parameters and initial conditions.

An example of using uncertainty analysis to probe parametric uncertainty in the fourier amplitude sensitivity test. This methodology explores the parameter space by a search curve that scans entire parameter space using oscillatory functions that are mutually orthogonal. This method was applied to a model of *aedes aegypti* population dynamics, and they found that uncertainty analysis provides an approach for identifying those parameters for which more accurate estimates would improve model predictions.

WEDNESDAY, November 16, 2016:

Diagnostics for Fast Model Estimates

Dave Campbell (Simon Fraser University)

Dr. Campbell discusses approaches for model estimation that fall in the middle of “quick and dirty” Laplace approximation strategy and “slow and precise” MCMC strategy. He considers a noise infused state space model that tracks the annual population size of salmon. The model consists of two layers: the observation process and the latent or unobservable state equation. The noise in the unobservable layer may be used to account for un-modelable environmental fluctuations or random perturbations to migratory routes. Subsequently, the population size is observed via noisy measurements, where this may be due to challenges in accurately counting the size of the population of salmon. As a result, estimating parameters through these two layers of noise requires dealing with considerable uncertainty. The target of this work is to develop a probabilistic integration approach.

The widely adopted Integrated Nested Laplace Approximation (INLA) is designed to approximately integrate out some parts of the model, accelerating and simplifying the process of estimating parameters. The INLA approximation lies in the assumption that performing the integral is equivalent to integrating a Gaussian. The traditional alternative to using INLA, typically requires high dimensional and slow but very accurate Monte Carlo integration. Dr. Campbell and his colleagues have devised a new INLA alternative model integration approach that provides the user the flexibility to choose between speed and accuracy on a continuous spectrum. Additionally, the proposed approach outputs a measure of confidence in the applied approximate integral and serves as a diagnostic for when INLA provides an acceptable approximation. Dr. Campbell presented results from a one-dimensional model to illustrate the method, but pointed out that the approach can reasonably scaled up to 10 dimensions or more. This is joint work with Charlie Zhou (Simon Fraser University) and Oksana Chkrebtii (the Ohio State University).

Covariates in population models

Subhash Lele (University of Alberta)

Climate change and other human disturbances affect wildlife populations. Population dynamics models are basic to studying extinction risk and management strategies. Dr. Lele discussed incorporating covariates into population dynamics models as a way to reduce the amount of error that is unaccounted for. He used data collected on how a San Joaquin kit fox population varied with rainfall to illustrate the basic approach along with remaining open questions.

Dr. Lele pointed out that parameterization of the model affects how covariates may be incorporated. Rainfall, for example, is likely to affect the growth rate of the kit fox population through the availability of the prey species but may also affect the carrying capacity of the habitat. How the covariate is included in the model can have a substantial influence on the predictions produced. Dr. also discussed the open question of how to project covariates into the future. This involves introducing another model for the covariate process and one must consider covariate measurement error as well as prediction error.

Multiscale Systems Biology: From Genes to Environment

Juan Gutierrez (University of Georgia)

Dr. Gutierrez's goal for the talk was to report fundamental questions. He used Malaria to provide context for illustrating the following questions:

- How to create a quantitative connection across scales?
- How to store and share data and models?
- How do we train scientists capable of undertaking a holistic study of ecology?

Dr. Gutierrez began at the population level by describing a SEYAR model for malaria that takes a standard SEIR model but splits the infected into symptomatic and asymptomatic. This model predicts that vaccination efforts could be effective for outbreaks in Columbia but not for outbreaks in Nigeria based on R_0 values computed from parameter estimates for the two regions. The next question is then why are some individual symptomatic while others are asymptomatic.

Dr. Gutierrez described a hemodynamic model that can reproduce the three clinical states: Immune, periodically infected, and healthy. Depending on parameters, the model can predict immunity, a mild (asymptomatic) infection or a severe (symptomatic) infection. Dr. Gutierrez then described experiments aimed at reconstructing a biochemical network that determines the parameters of the hemodynamic model. Dr. Gutierrez argued for using a standardized set of data structures provided by ModelDB to facilitate sharing of data across fields as well as a web-based information system called ALICE to tailor sequences of educational modules to the needs of individual students as a way to train scientists.

Enhancing predictability of biological models with structural sensitivity: how should we proceed?

Andrew Morozov (University of Leicester)

Because the underlying equations governing complex ecological systems is often unknown, it is important to test the sensitivity of predictions from a given mathematical model to variations in the form of the model (formulation of growth rates, functional responses, mortality terms, etc...).

Dr. Morozov discussed how one can quantify and estimate uncertainty in predictions from biological models that are structurally sensitive. The main idea of the general structural sensitivity analysis is to choose a set of base functions and project the initial infinite dimensional neighborhoods in functional space onto a finite dimensional space with coordinates consisting of the specific required values of the functions and their derivatives. He illustrated the approach with a predator prey model, showing that the more traditional approach of choosing a

parameterization for an unknown function could result in the misleading conclusion that the equilibrium of interest in the model is always unstable.

Matchmaker, Matchmaker, make me a match: migration of populations via marriages in the past

Mason Porter (University of California, Los Angeles)

Dr. Porter used data on movement of brides over the past 750 years from Korean family books to study human migration patterns via marriage. In the analysis, this high temporal resolution but low spatial resolution data on individual migrations was complemented with high spatial resolution but low temporal resolution data from modern censuses. The hypothesis that geographical distance plays a major role in population flux between family clans was tested by fitting the data from the family books to both a gravity flux model and a radiation flux model. The census data provides a method for developing a population flow network, quantifying the ergodicity of the clans in terms of how widely and uniformly they spread across Korea and identifying diffusive versus advective migration patterns.

THURSDAY, November 17, 2016:

Modeling Approaches for Simulating Infectious Diseases

Sara del Valle (Los Alamos National Laboratory)

The goal to predict outbreaks and epidemics before they occur. Realistically we can seek to accurately quantify an uncertain forecast once an outbreak has already been detected. This talk describes a modeling framework that simulates the movements, activities, and social interactions of disease spread influenced by social media data.

Emergent behaviors such as facemask usage and hand sanitizer can be extracted from social media data and then be used to inform models and quantify impact. The challenge is that for Twitter, only 1-2% of tweets carry a geotag, behavior is not demographically and geographically uniform. Wikipedia can also be used to track incidence, but it only tracks what language the article was read in. A Gaussian mixture model was created to probabilistically design a location for the social media data using the timezone and language to narrow down the possible locations. Results show that social media traffic correlates with disease incidence.

Disease Spread on Networks: Integrating Structure, Dynamics, and Data

Joseph Tien (The Ohio State University)

The study of population dynamics on contact and community networks has a long history in ecology and epidemiology. A central mathematical question is to understand how network structure and community characteristics combine to affect disease dynamics. Each community can be modeled by a susceptible, infectious, recovered (SIR) framework that includes an environmental pathogen reservoir. The communities are connected by pathogen movement and disease invasibility is determined by the basic reproduction number.

This talk shows that a generalization of the group inverse of the graph Laplacian matrix of the network plays a fundamental role in disease invasion and global stability. This generalized group inverse arises through a Laurent series expansion of a perturbation of the graph Laplacian L . Clustering of disease hot spots according to a generalization of the group inverse of the Laplacian matrix facilitates disease invasion.

The Predictability Horizon for Infectious Diseases

Samuel Scarpino (University of Vermont)

Predicting when and where diseases will spread requires a complex systems approach to modeling due to the multi-level interaction of hosts, pathogens, and their shared environment.

This talk investigates the question if such complex systems are even predictable.

Most diseases appear to be unpredictable beyond narrow time horizons, so it is important to use dynamic modeling approaches for prediction. Previous work has also shown that relying on past disease outbreak data can reduce the effectiveness of the model prediction. Instead, this talk suggests utilizing permutation entropy as a model independent metric of predictability. This method has identified a fundamental horizon for outbreak forecasts.

A social network study of isolation and influenza-like illness in the university setting: the eX-FLU study

Allison Aiello (University of North Carolina at Chapel Hill)

Few studies of the effectiveness of pandemic preparedness measure the community, outside of antivirals and vaccination. There is a lack of studies analyzing non-pharmaceutical interventions such as isolation: staying home, flexible work schedules, postponing mass gatherings and school closures. Yet it is hypothesized that university students would be protected if their social contacts and classmates voluntarily self-isolated at the onset of influenza-like illness (ILI) symptoms.

The eX-FLU study aimed to assess if isolation reduces ILI and lab confirmed respiratory virus transmission in social networks over the 10 weeks during influenza season. During the 10-week intervention period, there were 132 reported ILI cases in 110 individuals, where the 44 in the intervention group were asked to isolate themselves for 3 days and the 67 in the control group were not asked to change any of their behaviors. The results of the isolation intervention showed evidence that healthy contact of isolated ILI cases had a lower likelihood of becoming an ILI case.

Lousy lessons learned: Parameter estimability in complex ecological models

Stephanie Peacock (University of Alberta)

The ability to estimate parameters of an ecological model can be limited by the data available or can be impossible because of issues of nonidentifiability in the model itself. In the former case, data cloning provides a statistical computing method for assessing the inestimability of model parameters due to insufficient information in the data and can inform study design to ensure adequate data is collected.

Dr. Peacock discussed the application of data cloning to parasite transmission of sea lice from farmed to wild juvenile salmon. In this case study, spatial data of louse abundance provides evidence of an increase of louse abundance in wild salmon near salmon farms. As a general takeaway, Dr. Peacock argued that assessing the estimability of ecologically relevant parameters should be a key step when designing studies in which fitting complex mechanistic models is the end goal.

FRIDAY, November 18, 2016:

Applying models to epidemics

Michael Johansson (Harvard)

Every public health decision is based on a model, and public health decisions can be informed by quantitative models. Recent epidemics of pathogens such as H1N1 influenza virus, MERS coronavirus, chikungunya virus, Ebola virus, and Zika virus, highlight the importance of epidemics on local and global scales. Modeling has long been used as a conceptual tool to describe epidemic dynamics and assess possible interventions. It is essential to build links between the research and decision-making communities. The framework for forecasting the next outbreak of a disease can be outlined in five steps: establish objectives and targets; identify, acquire, and simulate data; formulate models; evaluate predictions, and forecast.

When it comes to the state of dengue forecasting models, there are a couple of issues to consider. First, there are a lot of dengue models out there, and there is little sense of appropriateness of models for decision-making. Also, there are no quantitative models being routinely used for decision-making. In order to gain a better understanding, the dengue forecasting project has been initiated. The project consists of 16 teams with 3 targets and 8 years of data. The results showed that early season forecasting is challenging and big seasons are harder to forecast.

Connecting models to data for animal movement models in ecology

Mark Lewis (University of Alberta)

Phenomenological models describe patterns at the same level they are observed while mechanistic models posit rules for interactions at one level of organization and then deduce patterns that emerge at another level. Animal movement patterns have long fascinated mathematicians and ecologists alike, and connecting movement models to data can be a challenging task.

Mechanistic home range models are based in individuals that have random and biased components of motion. Biased components are directed towards den/rendezvous sites. One study found that rate of biased movement is proportional to density of foreign scent marks which are deposited at an underlying rate that is increased in the presence of foreign scent marks.

Resource selection models correlate space use with available habitat type while step selection models correlate movement decisions over fixed time steps with available habitat type, and also include step length and turning angles. Both types of models allow the inclusion of detailed habitat features based on geographical information systems. SSM can be approximated with PDEs and this allows for simple analytical approximations for resource selection. However, the approximations can break down especially when step and length and turning angle differ in different habitat types. To remedy this break down, coupled step selection models were developed to incorporate nonlinear interactions between individuals which helps constructs a statistical foundation for testing hypotheses with these models.

Spring Workshop 1 - The Biological Challenges in Morphogenesis **(February 20-24, 2017)**

Organizers: Ann Burke (Wesleyan University), Jukka Jernvall (University of Helsinki), Stuart Newman (New York Medical College), Frederik Nijhout (Duke University)

Report by: Punit Gandhi, Colby Long, Thomas Woolley

MONDAY, FEBRUARY 20, 2017

Introduction and D'Arcy Thompson

Frederik Nijhout (Duke University) and Stewart Newman (New York Medical College)

This year is the 100th anniversary of D'Arcy Thompson's "On Growth and Form." A major theme of this influential book can be summed up by the quote "Forces in nature shape organic form." The book focuses on the interaction of biological entities with their environment through physical force. Dr. Nijhout pointed out that while "almost nothing in the book is true, ... [it] inspired a great amount of research." Dr. Newman claimed that while D'Arcy Thompson did not consider genetics or evolution, the spirit of Thompson's work is still with us even in the post-genetic world. Dr. Newman provided an example of this in the form of the proposition that Metazoan form originated and rapidly diversified by the action of Dynamic Patterning Modules (DPM). His recent work shows evidence that evolution acts to add more DPM over time and that this can also lead to similar structure in different places in biological form. Dr. Newman also announced that a special issue of the journal "Development" titled "On Growth and Form - 100 years on" is accepting submissions.

Achilles and the Tortoise: Physical constraints on logical models

Scott Gilbert (Swarthmore College)

Mathematical and physical models are abstractions, and, as such, always leave something out. Sometimes this is necessary for the model to function and that which is left out can be regarded as extraneous. In other cases, that which is left out is critical to the phenomenon being modeled and leaving it out causes problems in relating the model to observed reality. In his talk, Dr. Gilbert discussed some of these challenges in biological modeling as well as what he called "the dangers of mathematical models as the telos of all science." He enumerated several of these dangers and discussed how they might apply to present-day biologists. For example, he demonstrated how mathematical models are limited by the paradigm of their time by relating how Lord Kelvin had used a thermodynamics argument in the 19th century to argue that the earth was only 100 million years old.

Dr. Gilbert also cautioned against taking models too literally. Quoting Ian Barbour, he reminded us that models are "...an imaginative tool for ordinary experience, rather than a description of the world." He gave several examples, such as the epigenetic landscape of Waddington, a model that is useful despite not literally corresponding to anything in the physical world. Finally, he concluded by pointing out that many biologists implicitly hold the belief that biology is a science only in so much as it applies mathematics. He discouraged this way of thinking, as he argued it may cause biologists to ignore important details for the sake of mathematical elegance.

MorphoGraphX, a software to quantify morphogenesis

Richard Smith (Max Planck Institute for Plant Breeding Research)

One of the key components for understanding morphogenesis is being able to quantify the system under development. Critically, much of the biological data comes in the form of spatial microscopy. Full 3D imaging is desirable; however, this is often technically challenging in opaque tissue. Equally challenging is the modeling of growth and cell division in full 3D. Fortunately, many biological processes occur on surface layers of cells, and 2D models can be used. However, these surfaces are often not flat and capturing the underlying geometry of the space may be key to understanding the dynamics of the layer. For example, it has been seen that rate of cell division often depends on the local curvature.

In his talk, Dr. Smith introduced the open-source software program MorphoGraphX that enables the extraction of curved surface meshes. Further, it includes a suite of algorithms that allow the data to be manipulated and segmented, allowing the mesh to be augmented with extra data of local cell characterization. Finally, using semi-automatic, inbuilt toolboxes, MorphoGraphX is able to track cellular data temporally, allowing the user to characterize growth and morphology.

Beyond the capabilities of simply being able to generate accurate representations of the data, it is desirable to work on these meshes. For example, a user may want to include prescribed dynamics such as growth, cell division, and even molecular kinetics. MorphoDynamX addresses exactly these desires. Namely, using a friendly GUI interface, a user can quickly generate a modular description of dynamics occurring on an extracted mesh. Such *in silico* experiments then have the ability to suggest the underlying mechanisms generating the tissue's growth and function.

Differential tissue tension as a mechanism for balancing deep conservation and lability: recent results from experiments on chick digit morphogenesis

Kathryn Kavanagh (University of Massachusetts Dartmouth)

A major goal of evolutionary developmental biology is to identify whether there are rules governing the generation of phenotypic variation and how these might impact evolvability. Some of the most recognizable evolved differences among taxa are variations in the number and/or size of iterative segments in digits, known as phalanges. In her talk, Dr. Kavanagh presented evidence for a very deeply conserved skeletal module constraining the morphology of digit phalanges.

Phalanges form by a process of sequential segmentation. Cells are added continuously to the distal end. When the newly formed cartilage reaches a critical length a joint is initiated behind the growing tip, establishing a phalanx behind the new joint and growth of the digit continues distal to the new joint.

In her research, Dr. Kavanagh measured the sizes of the first, second, and third phalanges (P1–P3) of multiple different birds. She then plotted the ratio of P3/P1 versus the ratio of P2/P1 for each bird to create a morphospace. Strikingly, the plotted ratios all fell along a straight line. With knowledge of this relationship, one can predict the size of P3 accurately by knowing the sizes of P1 and P2. Amazingly, when the fourth phalange was added to the measurements and more bird species were considered this relationship carried over to the third dimension, with all the data lying within a given triangular subspace. Critically, this triangular morphospace can be separated into birds with different uses for their digits, e.g. digging, perching, etc.

Overall, these data provide a better understanding of how the properties of developmental systems work in combination with natural selection to guide evolution of skeletal proportions in vertebrates.

From molluscan shell growth to epithelial morphogenesis: the influence of D'Arcy Thompson
Severine Urdy (University of Zurich)

Dr. Urdy used the examples of (1) growth and evolution of mollusk shells and (2) growth and regulation in mammalian (MDCK) cells to highlight that the core of the field of evolutionary developmental biology lies in the intuition that the way tissues grow during embryonic development, the way they sustain their structure and function throughout lifetime, and the way

they evolve are closely linked. The first example was an experimental study that followed the growth of mollusk shells for 18 months to understand how growth dynamics leads to variation in spike length. In the spirit of D'Arcy Thompson's work, Dr. Urdy and collaborators found an unsuspected effect of geometry on the growth process: the curvature of the shell plays a role in shell ornamentation by affecting the ribbing pattern. The second example focused on time-lapse experiments to study epithelial morphogenesis using MDCK cells cultured in 3D in vitro. Dr. Urdy and collaborators developed a stochastic cell-based model based on Bertalanffy (1938) that was inspired by D'Arcy Thompson and highlights the importance of growth dynamics, especially in individual data, to understand the intricate relationships between growth and form.

Dental phenotypic complexity and the deep historical roots of the intersection of morphogenesis and evolution

Kate MacCord (Arizona State University)

Ms. MacCord used the history of theories for morphological differences in mammalian molars as an illustration of differing viewpoints at the intersection of morphogenesis and evolution -- an intersection that is increasingly at stake for modern day practitioners of evolutionary developmental biology and developmental evolution. The focus of her talk was on the conflict that erupted over molar development between Henry Osborn who developed the tritubercular theory and Carl Rose who proposed the concrescence theory.

Osborne implicitly assumed a weak form of the biogenetic law that ontogeny recapitulates phylogeny while developing the tritubercular theory that mammalian tritubercular molars evolved from simple reptilian cones on evolutionary timescales. Rose's concrescence theory, on the other hand, described the development of molars through concrescence of initially independent cusps on a developmental timescale. At the root of the conflict between these two theories that are not necessarily incompatible was the implicit belief of Rose in the strong form of the biogenetic law that phylogeny causes ontogeny. Implicit assumptions on both sides also lead to the failure of either theory to properly account for development: the specific mechanism for concrescence was never explained and the tritubercular theory kept development as black box.

From Networks to Function – Computational Models of Organogenesis

Dagmar Iber (ETH Zurich)

Dr. Iber provided an overview of her lab's work on growth and size control in organs, patterning on growing domains, epithelial organization, and branching patterns during organ development. The overall challenge tying the work together is to integrate models and data across scales.

The first project she discussed was using the dilution of the cytokine Unpaired (Upd) as a possible mechanism to explain measurements of an area dependent decline in growth rate of the *Drosophila* eye primordium. Dr. Iber then turned to the developing *Drosophila* wing imaginal disc where experimental data and simulation results indicate that pre-steady-state dynamics are a probable mechanism for dynamic scaling of morphogen gradients. Her group also used data from the *drosophila* wing disc to study epithelial organization. They find that under the assumption that cell division occurs at random sizes, a cell-based simulation using the software LBIBCell reproduces the predicted distribution of cell shapes. Finally, Dr. Iber discussed the

differences in branching patterns in the lung and kidney and provided a model based on a Turing mechanism that creates a pre-pattern on which the branching pattern can grow robustly.

TUESDAY, FEBRUARY 21, 2017

The two-galectin tetrapod limb patterning network: synergies of experiment, modeling, and phylogenomics

Stuart Newman (New York Medical College)

The skeletal elements of tetrapod limbs are preceded in development by cartilage elements which form at where mesenchymal cells condensate into high concentration regions in the embryonic limb buds. Dr. Newman presented experimental evidence that CG (chicken galectin)-1A and CG-8 constitute a multiscale network that is a major mediator, earlier-acting than any previously described, of the formation and patterning of precartilage mesenchymal condensations in the developing limb. This network functions autonomously of limb bud signaling centers or other limb bud positional cues. He then presented a model consisting partial differential and integro-differential equations that qualitatively and quantitatively agrees with experimental results of network perturbations. A reduced version of this model highlights that the morphodynamic pattern forming process is tied in with cell motion and illustrates a pattern forming mechanisms in which widely separated diffusion coefficients is not necessary. Finally, Dr. Newman discussed recent work to understand the evolutionary origin of this network by looking more generally at vertebrates with paired appendages.

Morphogenesis of the body wall across vertebrates

Ann Burke (Wesleyan University)

Enclosing the gut and its derivatives within the coelom is an essential and universal process of vertebrate embryogenesis. This morphogenesis occurs as somitic and lateral plate mesoderm (LPM) populations interact forming a muscular body wall that fuses at the ventral mid line. The dynamic boundary between somites and LPM is called the lateral somitic frontier (LSF), and Dr. Burke discussed observational work to map the LSF in the body wall of embryos representing a range of vertebrate crown groups. She and her colleagues found that changes in the topography of the LSF and the proportion of primaxial and abaxial domains are correlated with major locomotor adaptations. In particular, LSF is the boundary between two connective tissue lineage domains in the body. The early vertebrate body wall was primaxial. The origin of paired appendages is correlated with a persistent somatopleure, the LSF, and an abaxial domain.

A new model of early primary palate morphogenesis

Marta Linde-Medina (University of California, San Francisco)

The amniote face develops from several primordia that form around the primitive mouth. These primordia extend along different axes to eventually meet and fuse to form the embryonic face. A main goal in the field of craniofacial development is to understand how these buds extend during early stages of morphogenesis, because disruptions to this process can lead to clefting.

The extracellular matrix (ECM), which is thought to play a passive role in early primary palate morphogenesis may actually be a driving force during development. It is known that fibroblast growth factor (FGF), which leads to clefting, alters cell proliferation and cell polarity. Dr. Linde-Medina and her colleagues have experimentally shown that FGF signaling additionally

alters the components of the ECM. Based on this result, she presented a model that predicts that ECM plays a key role in two ways: (1) by changing the mechanical pliability of the epithelium, allowing or constraining budding outgrowth at certain regions, or (2) by generating a pulling force that evaginates the epithelium. Dr. Linde-Medina also presented preliminary experimental measurements in support of this theory.

Morphogenesis of wing shapes in Lepidoptera

Frederik Nijhout (Duke University)

The wings of different species butterflies and moths differ greatly in size and shape. In all species the wings start as a small crescent shaped “imaginal disk” during the caterpillar stage, and gradually grow and change shape over a period of a few days to achieve the characteristic adult morphology. The developing wing is made up of two flat sheets of cells, making up the dorsal and ventral surfaces, respectively. Morphogenesis of the wing is due to directional growth and Dr. Nijhout's experimental observations indicate that this is best explained by a changing and species specific spatial pattern of cell division that is likely controlled by spatial patterns of ecdysone-receptor expression. In this talk, he explained how observations of mitotic orientation show no evidence of cell division significantly different from random in various locations across the wing. Moreover, simulations that rely on directional cell division are unable reproduce the observed patterns of growth. Instead, as Dr. Nijhout explained, actin networks constrain the direction of growth and keep wing veins parallel during development. The final details of shape are controlled by the shape of the bordering lacuna and patterned cell death.

The development of vertebrate lateral line electroreceptors

Clare Baker (University of Cambridge)

Around the nose, eyes, and gills of many fish are electroreceptors known as ampullary organs, which are able to detect weak electric fields. Electroreception is an ancient subdivision of the lateral line sensory system found in all major vertebrate groups (though lost in frogs, amniotes and most ray-finned fishes). Electroreception is mediated by 'hair cells' in ampullary organs, distributed in fields flanking lines of mechanosensory hair cell-containing neuromasts that detect local water movement.

Despite similarities of neurophysiology and innervation, the embryonic origins of ampullary organs in different species remain controversial. For example, in bony fish it is thought that the organs are derived from lateral line placodes, whilst in cartilaginous fish it is thought that they stem from a neural crest origin. In her talk, Dr. Baker presented morphological and molecular data describing lateral line system development in the bony fish, “Mississippi Paddlefish,” which demonstrate a lateral line placode origin for ampullary organs and neuromasts. She explained how long-term in vivo fate-mapping has shown that the homology of electroreceptors and ampullary organs is conserved in cartilaginous fishes.

She also presented more recent work developing the molecular origins of the ampullary organs. Specifically, the homology was compared between the Mississippi paddlefish (which is electroreceptive) and the zebrafish, which has a similar development, but is not electroreceptive. By investigating important signaling pathways for neuromast development, and by using RNA-seq to generate a lateral line organ-enriched gene-set, she has illuminated the processes behind ampullary organ development, physiology and evolution. Critically, the actions of the Wnt,

Notch and Fgf pathways seem to be opposite in these two species. However, more work is needed to fully understand this seemingly reversed structure.

Integration and the developmental-genetics of the face

Benedikt Hallgrímsson (University of Calgary)

Despite the tremendous progress made in recent years towards understanding fundamental developmental mechanisms, we know very little about the genetic or developmental causes of phenotypic variation within species or among related species. This is a central area for evolutionary biology as phenotypic variation is the raw material on which evolution acts. It is also an area that has important implications for understanding etiologically complex malformations such as cleft lip and palate. Such malformations occur at the extremes of multifactorial phenotypic distributions and must be understood within the same theoretical framework as other aspects of variation.

At the phenotypic level, the complexities of the genetic to phenotypic translation can be grouped into two phenomena:

- 1) canalization is the tendency for development of a specific genotype to follow the same trajectory under different conditions (different environment or different genetic backgrounds);
- 2) morphological integration refers to the tendency for structures to show correlated variation because they are affected by shared developmental processes.

Critically, the relationship between genotype and phenotype is both complicated and simplified by these phenomena. Specifically, canalization suppresses the phenotypic effects of genetic variants and gene interactions, which greatly complicates the genetics of complex traits, confounding prediction of variation. On the other hand, the convergence created by morphological integration simplifies genotype-phenotype maps.

In order to understand variability, Dr. Hallgrímsson investigated craniofacial forms using techniques combining developmental genetics, bioinformatics, 3D imaging, and morphometrics. Using multiple species, including humans, macaques and mice, he discovered new phenotype-genotype mechanisms. For example, his research demonstrated new connections between Fgf regulation and head length control.

WEDNESDAY, FEBRUARY 22, 2017

Species transformations

Jukka Jernvall (University of Helsinki)

Hybridization is well known to occur between living taxa, and can be considered a biological transformation of related forms. In mammals, hybridization has attracted renewed interest due to paleogenomic evidence that has implicated interbreeding among human taxa. In his talk, Dr. Jernvall gave an example related to the question of whether hybridization between morphologically disparate taxa can produce developmentally stable, intermediate morphologies. The example he used involved two related species of pinnipeds, grey seals and ringed seals. The teeth of the two species were studied alongside those of a unique hybrid specimen of the two species. Grey seals have fang-shaped post-canine teeth with a prominent central cusp and, when present small accessory cusps. In contrast, ringed seal post-canines have multiple slender cusps.

Rather than mathematical transformations, a computational model simulating tooth development was used to explore the developmental and genetic nature of the hybrid morphology. First, a model of tooth development was used to find two sets of parameters that produced the types of teeth seen in grey seals and in ringed seals. Surprisingly, simply averaging these quantitative parameters in the model produced teeth phenotypically similar to those found in the hybrid specimen. This finding suggests that none of the genetic traits involved in tooth formation in either species is dominant over any other. Dr. Jernvall then concluded his talk with a discussion about the implications of this research towards detecting hybridization in human ancestors. As he explained, with only morphological data available in the fossil record, it may be very difficult to detect these intermediate morphologies and differentiate new species from hybrids.

Cell-fate determination in the transition to multicellularity

Mariana Benitez (National Autonomous University of Mexico)

The transition to multicellularity is a major evolutionary event which has occurred at least twenty-five times in different lineages. In her talk, Dr. Benitez discussed two different proposed models of how multicellular organisms form. One type of model assumes that some cells in a cluster differentiate and but that the different types of cells stay together. The other models assume that different types of cells aggregate to form a structured mass. Many attempts to model the evolution of cell types in multicellular aggregates fail to take into account how the cells interact with their environment and with one another. This essentialist view of cells attributes properties of the system to the individual cells when they may in fact be properties of the interaction between many cells.

Dr. Benitez presented her results modeling multicellular aggregates using dynamical patterning modules (DPMs). The DPM framework takes into account the cellular environment by assuming only that there are different types of cells exhibiting properties such as adhesion and intercellular communication. She showed how these models contain all of the necessary ingredients to account for robust cell differentiation and patterning in the aggregation of cellular masses. As she explained, this offers an alternative explanation for differential complexity in cells and suggests DPMs are a useful framework for understanding developmental processes and the transition to multicellularity.

Exposing the cryptic mechanics of morphogenesis: integrating signaling and mechanics during axis elongation

Lance Davidson (University of Pittsburgh)

Axis extension in vertebrates serves to convert a sphere or disk of cells in the early embryo into a long body plan that resembles that of the adult. By contrast with later morphogenetic movements that shape complex 3D structures, axis extension proceeds as a relatively simple rearrangement of cells in the plane. However, movements are coordinated between multiple layers of mesenchymal and epithelial cells, each undergoing independent rearrangements. In his talk, Dr. Davidson discussed his lab's work in developing a complete set of experimental tools and theory for direct biomechanical analysis of these movements. Using the elongating dorsal tissues of the *Xenopus* (a genus of frogs) embryo, they have discovered several surprising findings about the coupling between the processes that generate forces needed for extension and the processes that regulate spatial and temporal mechanical properties of the embryo.

Forces and material properties can be coupled in a positive fashion that preserves rates of morphogenesis or can be negatively coupled to alter rates of morphogenesis in response to changing environmental conditions. Both mechanisms highlight basic elements of robust control networks that couple mechanics and cell signaling pathways and underlie the morphogenetic programs that drive self-assembly.

Excitable dynamics and Yap-dependent mechanical cues drive the segmentation clock
Olivier Pourquie (Harvard Medical School)

The periodic segmentation of the vertebrate body axis into somites, and later vertebrae, relies on a genetic oscillator (the segmentation clock) driving the rhythmic activity of signaling pathways in the presomitic mesoderm (PSM). This segmentation clock controls both the length and total number of somites, both of which vary between species. While the clock is often presented as a population of phase-entrained oscillators, whether its oscillations are an intrinsic property of individual cells or represent a population-level phenomenon is not known.

In his talk, Dr. Pourquie discussed the results of several experiments conducted with Alexis Hubaud that indicate these oscillations are a complex population-level phenomenon. Using a novel in vitro system in which sustained oscillations can be maintained, they showed that oscillations are a collective property of PSM cells which can be actively triggered in vitro by a dynamical quorum sensing signal involving Yap and Notch signaling. Their work demonstrates that manipulation of Yap-dependent mechanical cues is sufficient to predictably switch isolated PSM cells from a quiescent to an oscillatory state in vitro, a behavior reminiscent of excitability in other systems. Taken together, their work suggests that the segmentation clock behaves as an excitable system, introducing a novel paradigm to study such dynamics in vertebrate morphogenesis.

Blood flow and cardiac morphogenesis: A deterministic relationship?
Sandra Rugonyi (Oregon Health & Science University)

Congenital heart disease appears in around 1% of newborn babies in the U.S. and is the leading non-infectious cause of death among infants. Critically, very few genetic defects are known to underlie cardiac malformations. In her talk, Dr. Rugonyi hypothesized that, rather than being genetic, a number of cardiac problems could stem from abnormal hemodynamic conditions during development.

Her research was performed on chicken embryos because they are easy to manipulate and because the genetic processes of interest are highly conserved across vertebrate species. Most importantly, many heart defects found in chickens are also observed in humans. She altered the blood flow around the heart of chicks in two ways. Either the flow going into the developing heart was stopped from one of the veins, or, a suture was added to the artery leading away from the heart, which restricted, but did not stop, the outflow of blood.

Not only did these interventions generate many different types of developmental defect, but the type of defect often correlated with the type of intervention that occurred. Namely, certain defects occurred when in flow was reduced and certain defects were only seen when the outflow

was restricted. Further, because the restriction of the suture was variable, it was found that the amount of restriction also appeared to correlate with the appearance of certain defects. Of those chicks whose hearts appeared to develop normally the cellular populations around the heart were significantly changed, which could lead to problems as the chicken matures. Taken together these data suggests that blood flow is a strong determinant of cardiac tissue growth and remodeling.

Mechanical models of plant morphogenesis

Richard Smith (Max Planck Institute for Plant Breeding Research)

Plant cells are like small balloons, inflated with turgor pressure that is contained by a rigid cell wall. This turgor pressure is considerable, often 5-10 bar, and it gives green plant tissues their structural stability and form. It is also the driving force behind plant cell growth, which can be seen as a stress relaxation process of the cell wall. Since the stress in a pressure vessel depends on its shape, the geometry of individual cells can have a profound impact on the mechanical behavior and growth of the tissue. In his talk, Dr. Smith presented two projects which tried to elucidate the counterintuitive results behind the formation of plant organs from individual cell encoding.

The first project involved understanding the shape of root hairs. In particular, it is assumed that growth hormones are produced at the tip of the root, but, paradoxically, the part that is seen to grow the most is produced at a region behind the root tip. To study this conundrum, Dr. Smith developed a finite element method simulation of the root. His growth rule took into account both the concentration of growth hormone and the cell strain. The result is that cells at the tip do not grow particularly large because they are not yet pressurized, rather it is the cells that are developing behind the tip that are subject to both effects of high growth hormone and large stresses. Hence, Dr. Smith's simulated morphologies reproduce the experimentally observed forms.

The second project involved understanding the shapes of plant cells. There is a cell shape, known as the puzzle cell shape, which is asymmetrical and has large lobe structures that point out in different directions. These puzzle cells are tightly packed together like puzzle pieces in the plant. Again, using dynamic simulations of microtubule formation, Dr. Smith showed that these puzzle shaped cells are able to reduce the pressure on their cell walls. This illustrates that plants are able to use multiple strategies for reducing cell wall pressure in their cells.

THURSDAY, FEBRUARY 23, 2017

From the planar polarity of cuticular hairs to factors in insect cuticle hydrophobicity

Paul Adler (University of Virginia)

The cuticular exoskeleton of insects such as *Drosophila* is decorated with a variety of structures. Some of these are sensory (e.g. sensory bristles) while others are not innervated (e.g. cuticular hairs or trichomes). Much of the cuticular surface is covered by hairs and in any body region these display a consistent planar polarity. This has best been studied on the wing where each epithelial cell produces a single distally pointing hair. The initial development of each hair is formed by a cytoskeletal mediated outgrowth that forms at the distal edge of each cell. The

proteins of the fz/stan pathway that regulates this all accumulate asymmetrically in wing cells prior to hair outgrowth. A number of models have been suggested to explain how this pathway restricts the activation of the actin cytoskeleton to the distalmost part of the cell. In his talk, Dr. Adler discussed these models as well as evidence from his lab that there are multiple factors influencing the activation of the cytoskeleton.

Additionally, Dr. Adler presented research from his lab on the highly hydrophobic nature of insect cuticles. For example, when a *Drosophila* wing is dropped into water, it not only floats, it does not even wet. Two factors, surface structures (e.g. hairs) and the waxy coating of the cuticle have been suggested to be important for hydrophobicity. His lab has found that the wing does not become hydrophobic until shortly before the adult ecloses well after hair morphogenesis. He discussed this result as well as the basis for the lipid coating of the cuticle.

The basal end of cell and tissue morphogenesis in the *Drosophila* wing

Seth Blair (University of Wisconsin)

Many crucial events that regulate the development of the *Drosophila* wing, including junctional tension, growth control, and planar cell polarity, are concentrated in the apical region of the wing's epithelial cells. In recent years Dr. Blair's laboratory has worked on these apical events, and especially the role of the apically localized protocadherins Fat and Dachshaus and their downstream effectors. However, in this talk, he presented some of their research examining the roles of the basal end of these cells, which are equally critical for various signaling and morphogenetic events. He presented data on the basal extracellular matrix, the extracellular matrix metalloproteinases, and the basal cell processes of imaginal discs and pupal wings and their abilities to regulate BMP signaling, wing disc morphogenesis, and the peculiar basal-to-basal tubulogenesis of wing vein formation.

The emerging mechanome of gastrulation: Results, questions, and problems, mostly the latter

Ray Keller (University of Virginia)

In his talk, Dr. Keller summarized what is known of the molecular and cellular mechanisms of the major regional morphogenic machines of amphibian gastrulation. He discussed in detail the dynamics of expression and the mechanical and regulatory integration of two of these mechanisms, convergent extension and convergent thickening. These processes refer to the narrowing and lengthening of tissues by internal forces generated by cell intercalation. The theme of his talk was "how embryos put their players on the field," meaning, how are the large scale spatial patterning and timing of cell behaviors influenced by the mechanical context (forces, anchorages, tissue stiffness) inside the cell. The evidence suggests that the large scale mechanical linkages and spatiotemporal patterns of expression of regional processes are as important as local cell behaviors for the function and evolution of gastrulation. For example, Dr. Keller explained the role of an actomyosin network cytoskeleton which generates forces in the cell that drive gastrulation.

Forces and their regulation during dorsal closure in *Drosophila*: A model system for cell sheet morphogenesis

Dan Kiehart (Duke University)

Dorsal closure is a morphogenetic process in the fruit fly *Drosophila melanogaster* that models cell sheet movements and shape changes in vertebrate wound healing, neural tube closure, and

palate formation. Defects in vertebrate cell sheet movements lead to spina bifida, cardio bifida, and cleft palate in vertebrates. Many of the proteins involved in cell sheet movements are highly conserved between flies and humans; some are more than 90% identical and many human proteins can experimentally rescue the genetic defects caused by mutations in their fly counterparts.

In his talk, Dr. Kiehart explained the diverse methods that his lab is using to study dorsal closure in order to investigate the basic biology of cell sheet morphogenesis. One of their methods is gene discovery, in which they try to determine which genes are required for cell sheet movements in closure. They also use biophysical interrogation of the mechanobiology of morphogenesis to determine the forces that drive cell shape changes and cell sheet movements. For example, one of their methods is to use lasers to cut various structures around the dorsal closure. The behavior of the closure after these structures are cut enables them to test hypotheses about the mechanics involved. Dr. Kiehart also showed 4D images (3D images of the sub-cellular distributions of fluorescently tagged proteins taken over time) that documented the movements involved in closure on a wide range of time and length scales.

MechanoDevo: How growth and form derived mechanical forces channel plant morphogenesis

Olivier Hamant (University of Cambridge)

Using recently developed live imaging and modeling techniques, Dr. Hamant presented work on the relation between mechanics and shape changes in plants in which morphogenesis is mainly determined by cell walls. The control of cell division plane orientation is crucial in plants, in which cells cannot rearrange their positions, as they are glued to each other by their cell walls. Cell geometry has long been proposed to determine cell division plane orientation but Dr. Hamant showed that, in the Arabidopsis shoot apex, plant cells instead divide along maximal tension. The shape and growth-derived forces inducing this tension act as signals that orient plant microtubules. In addition to cell division direction, this response channels key biological features such as cell shape and final organ shape. Beyond microtubules, such forces also contribute to cell polarity and to the expression patterns of master regulators of meristem maintenance. The implications of this work are numerous and include a role of mechanical conflicts emerging from growth heterogeneity in the reproducibility of shapes. Altogether, this provides a picture in which mechanical forces add robustness to plant morphogenesis by channeling the dynamics of cell effectors and molecular pathways.

Bioelectrical patterns instructing growth and form: introducing a modelling platform elucidating molecular mechanisms of developmental bioelectricity

Alexis Pietak (Tufts University)

In his talk, Dr. Pietak explained a new physiological simulator of how dynamics facilitate the development of bioelectric-pattern control strategies. The simulation package, known as BETSE, is able to predict bioelectric patterns and their spatio-temporal dynamics by modeling ion pump, channel, and gap junction activity. The simulator also allows for the flexible definition of continuous gene regulatory network models, which are functionally integrated with bioelectric signaling mechanisms.

To demonstrate the simulator, Dr. Pietak presented an example of how the planarian flatworm forms. The shape of an animal body plan is constructed from protein components encoded by the genome. However, bioelectric networks composed of many cell types have their own intrinsic dynamics, and can drive distinct morphological outcomes during embryogenesis and regeneration. Planarian flatworms are a popular system for exploring body plan patterning due to their regenerative capacity. Namely, if they are cut in two they will regenerate their head and tail in the correct respective halves. Critically, multiple interventions, including biochemical and bioelectric stimulation can alter the reformation of the head and tail polarization leading to worms with either two heads or two tails.

Ultimately, Dr. Pietak demonstrated that networks comprised of both genetic and bioelectrical circuits have unique capabilities that can explain key large-scale properties of biological growth and form. The BETSE modeling environment facilitates more realistic simulation of patterning systems, and supports quantitative models in a broad range of applications.

From genome to phenome: The developmental basis of mammalian variation

Karen Sears (University of Illinois at Urbana-Champaign)

Mammalian limbs provide a wonderful resource for the study of parallel evolution. Due to functional and structural requirements, mammalian limbs have converged multiple times on a rather limited number of morphologies. One of the most common parallelisms observed during the history of mammalian limb evolution is the reduction, or in extreme cases the loss, of skeletal elements. This is most commonly observed in the distal limb elements: the zeugopodia (the radius and ulna in the forelimb and tibia and fibula in the hind limb) and autopod (the digits). The developmental mechanisms responsible for digit loss have been well studied in many tetrapod groups, including mammals. In contrast, the developmental mechanisms behind zeugopodia reduction have received very little attention, except for a few studies within birds.

In this talk, Dr. Sears highlighted research into mammalian limbs that utilizes an integrative approach. Specifically, she examined a variety of test cases such as: bats, pigs, horses, moose, camels and mice in terms of the developmental basis of limb reduction. She showed that the most common pattern of reduction, that of reduced element width, is achieved via the same developmental process in both bat and mouse limbs (i.e., by a slower growth rate relative to other skeletal elements). This suggests that the parallel reduction of the posterior zeugopodia element within mammals could have occurred primarily by the repeated evolution of the same developmental mechanism. These findings also suggest that the developmental mechanisms behind the parallel evolution of other, more taxon-specific characteristics of limb reduction (i.e., element fusion) are not conserved.

Understanding the developmental underpinnings of limb formation can greatly increase our knowledge of the evolution of tetrapod limbs and provide hypotheses that can be tested using fossil data and molecular genetics.

FRIDAY, FEBRUARY 24, 2017

How mechanical forces create and loop the embryonic heart

Larry Taber (Washington University)

During development, the heart transforms from a single tube into a four-chambered pump. This transformation involves a dynamic interaction between genetic and environmental factors that regulate the primary developmental processes of growth (volume change), remodeling (property change), and morphogenesis (shape change).

For decades, it was commonly thought that the bilateral heart fields in the early embryo fold directly toward the midline, forming a cylindrical form. Recent experiments and models have challenged this view, however, suggesting a different folding mechanism, whereby the top corners of the tissue are folded diagonally towards each other through differential anisotropic growth between the mesoderm and endoderm.

After this heart tube has formed, it begins to loop into a c-shape to create the basic pattern of the mature heart. In his talk, Dr. Taber presented a cylindrical finite-element model to simulate the bending process in isolated hearts. He then compared the results of these simulations to actual experimental data. He compared the numerical stress and strain distributions in the model to those measured in cultured chick hearts and showed that there was reasonable agreement between the two. Finally, he presented an extended model that included realistic 3D geometry and the effects of external loads, including those exerted by the veins at the caudal end of the heart tube. Critically, if the pressure direction in the model is altered, the heart is oriented in the direction opposite to its wild-type configuration. Dr. Taber then showed that this prediction agrees with experimental evidence.

How cells move and die to shape the fly eye

Ruth Johnson (Wesleyan University)

While the photosensor cells for the *Drosophila* retina are recruited during the larval phase, the regular hexagonal structure of cells surrounding the photosensors develop during the pupal phase. Using live-imaging of the retina during the development of this hexagonal lattice Dr. Johnson's lab has uncovered a series of mechanisms involving local cell movements, competition, growth differentiation and apoptosis. In particular, her group has focused on a conserved adaptor protein Cindr that is crucial for eye development. Experiments show that this protein is involved in regulating the number of cells to be the same within each hexagonal structure on the eye lattice. Interestingly, she also described experiments she has done that show the hexagonal lattice can persist even when the signaling of apoptosis is disrupted and the cell numbers are no longer identical throughout the lattice.

Spring Workshop 2 - Modeling of Tissue Growth and Form **(March 6-10, 2017)**

Organizers: Mark Alber (University of California, Riverside), Dagmar Iber (ETH Zurich), Paul Kulesa (Stowers Institute for Medical Research), Philip Maini (University of Oxford)

Report by: Alan Veliz-Cuba, Hye Won Kang, and Yangyang Wang

MONDAY, March 6, 2017

The growth and patterning of the vertebrate neural tube

James Briscoe (The Francis Crick Institute)

In this talk, Dr. Briscoe talked about how distinct neuronal subtypes were generated in a precise spatial order from progenitor cells according to their location along the anterior-posterior and dorsal-ventral axes. Morphogen gradients emanating from the dorsal and ventral sides of the spinal cord establish in neural progenitors along the dorsoventral axis. In the vertebrate neural tube, the dorsoventral pattern of neural progenitors is specified by 13 spatially distinct transcriptional states. These are encoded by the combinatorial expression of transcription factors in response to opposing morphogen gradients – ventrally sonic Hedgehog (Shh) and dorsally secreted bone morphogenetic protein (BMP). These two signals act in a graded fashion to organize the pattern of neurogenesis. Cells perform equivalent of maximum-likelihood estimation using these two input signals, which can be captured by a decoding map. This provides a phenomenological model of the decoding of the two input morphogen gradients. Dr. Briscoe also provided a mechanistic explanation for the phenomenological model, through a 3-node transcriptional network, which appears to be consistent with the experimental data. More importantly, the network separates early gradient decoding from later differentiation phase, during which progenitor pattern is maintained despite the decrease in Shh and BMP signaling.

The relationship between growth and form in the developing limb bud

James Sharpe (Centre for Genomic Regulation)

The vertebrate limb bud is a classical model system for developmental biology, with the advantage of having been studied for many decades. However, a consensus model of its physical morphogenesis has not been reached. In this talk, Dr. Sharpe showed that previous ideas on the mechanical basis of limb bud elongation, including mechanical constraint from the ectoderm, proliferation gradient hypothesis, oriented cell divisions, distally – directed migration and motility gradient hypothesis, are not sufficient for explaining morphogenesis. He proposed his own hypothesis, intercalation convergent-extension, and introduced a 3D dynamical model (a Cellular Potts Model) which captures this hypothesis. Finally, he concluded that form is not driven by growth in the developing limb bud. Instead, he believed that intercalation would lead to growth-compensated convergent-extension.

Beyond apical constriction: vertical telescoping and other novel models of epithelial bending

Jeremy Green (King's College London)

Dr. Green provided evidence to support a theory firstly suggested in the 1950s by famous codebreaker and mathematician Alan Turing, by putting forward the idea that regular repeating patterns in biological systems are generated by a pair of morphogens that work together as an “activator” and “inhibitor”. He presented his experiments on the development of the regularly spaced ridges found in the roof of the mouth in mice, which identified the pair of morphogens working together to influence where each ridge will be formed: FGF (Fibroblast Growth Factor) and Shh (Sonic Hedgehog). These chemicals controlled each other's expression, acting as components of an activator-inhibitor pair in this system and therefore controlling the generation of the regularly spaced transverse ridge patterns of the palate. In fact, this study provides the first experimental identification of an activator-inhibitor system at work in the generation of stripes; in this case, in the ridges of the mouth palate. In addition, he discussed constraints on network topologies by stable periodicity and how the periodicity can allow the definition of low-complexity systems of more than two components. He also presented a temporal analysis which identified leading (Wnt-response, eFGF-response, Shh expression) and lagging components (BMP-response, mFGF-response, Shh-response).

Developmental mechanisms underlying the evolution of form and function in the jaw

Richard Schneider (University of California, San Francisco)

Dr. Schneider presented how the form arises during development and is related to the function in the jaw. For that, they compared the jaw anatomies of duck and quail experimentally and found that duck has a development of the secondary cartilage, but quail does not. The talk first focused on the role of the neural crest mesenchyme (NCM) which produces all cartilages and bones in the jaw skeleton. By transplanting NCM from quail to duck, the experiments showed that NCM decides the jaw skeleton pattern and causes a loss of cartilage on the coronoid process. Moreover, they found that Transforming Growth Factor-Beta and Fibroblast Growth Factor signaling also inhibits secondary chondrogenesis on the coronoid process. Putting these together, the hypothesis that the mechanical forces accompanied with NCM-mediated signaling and musculoskeletal anatomy also promote the formation of secondary cartilage was suggested and tested to get insights on the mechanism linking form and function during development and evolution.

Predicting principles of tissue growth and mechanics through the modeling of tooth morphogenesis

Miquel Marin-Riera (University of Helsinki)

Dr. Marin-Riera talked on what mechanism possibly drives cell movement and tissue deformation during mammalian tooth morphogenesis to predict how the morphological variation is produced in development. The mammalian tooth has a large variation across the phylogenetic tree, so it is an appropriate system to study for the goal. They developed and introduced a mathematical model for the tooth movement to study individual cell movement and underlying mechanism, which are caused by mechanical forces from tissue growth and cell to cell adhesion. The tissue-specific growth rates in the model were fit to the experimental data. Then, the model was able to predict that various adhesion strengths between different cell types can cause different spatial patterns of mechanical forces, and the prediction was validated using the experimentally inferred forces.

TUESDAY, March 7, 2017

Eyes, large and small: variation of eye size in *Drosophila* and beyond

Fernando Casares (Universidad Pablo de Olavide, Centro Andaluz de Biología del Desarrollo)

Animals are characterized by their morphology -to such an extent that most often we recognize different species for their unique shape and size. Since organs are the product of development, mechanisms must exist to ensure the constancy of organ size and shape within a given species. However, these mechanisms need also to be plastic, as organ morphology has varied -and in some instances, very remarkably- during evolution. In the lab Dr. Casares investigates the mechanisms that regulate organ size by studying the eyes of flies. “Eyes” because they are specialized sensory structures of great biological relevance; and specifically “of flies” because eyes have undergone an extraordinary morphological and functional diversification within this huge insect group -the diptera. Typically, flies possess two eye types: small dorsal eyes (called “ocelli”) and large, lateral eyes. Although the development of both eye types is controlled by the same morphogen, Hedgehog (Hh), Dr. Casares discussed the different strategies used by these

two eye types to control their small or large size. Dr. Casares also presented further work, that combines experimentation and mathematical modeling, aimed at identifying the changes in biological processes that might be responsible for the variation of eye size during evolution, and the limits to that variation.

Cell competition: a mechanism that promotes developmental stability

Laura Johnston (Columbia University)

Dr. Johnston presented results of experiments designed to reveal how Dilp8 and cell competition are functionally linked in a mechanism that promotes optimal animal fitness. Development is a robust process that yields remarkably reproducible body size and bilaterally symmetric appendages. In *Drosophila*, developmental stability is tightly regulated and even small deviations from bilateral symmetry - known as fluctuating asymmetry (FA) - are quite rare. During growth, cells within organs behave as social communities and use comparisons of cell fitness to foster cooperation. Cells perceived as unfit are eliminated from the tissue via cell competition, which promotes precise organ size control and optimal organ fitness. Mutations in genes required for cell competition lead to loss of bilaterally symmetric wings, increasing wing FA. Dilp8 is a secreted peptide that via its neuronally expressed receptor, Lgr3, coordinates tissue growth with developmental timing by gating ecdysone production in the prothoracic gland. Loss of dilp8 or lgr3 leads to strong FA in adult wings, and also prevents cell competition.

Mathematical modeling and image analysis of BMP-mediated patterning in developing zebrafish embryos

David Umulis (Purdue University)

Dr. Umulis explained that Bone Morphogenetic Proteins (BMPs) act in developmental pattern formation as a paradigm of extracellular information that is passed from an extracellular morphogen to cells that process the information and differentiate into distinct cell types based on the morphogen level. Numerous extracellular modulators and feedback regulators establish and control the BMP signaling distribution along the dorsal-ventral (DV) embryonic axis in vertebrates to induce space and time-dependent patterns of gene expression. To identify how the dynamic pattern is regulated during development, Dr. Umulis has developed a seamless data-to-model integration and optimization strategy. First, the nuclear intensities of fluorescently stained Phosphorylated-Smad5 (P-Smad) are acquired for each nuclei in each embryo from staged populations to provide a quantitative time-course for the BMP signaling gradient. Next, the nuclei are segmented to yield quantitative point-clouds of P-Smad level at each nuclei. The individual point clouds are registered to similarly staged embryos using a process called Coherent Point Drift (CPD) and the registered populations provide rigorous quantification of BMP signaling. To delineate the mechanism of BMP signal inhibition by the secreted binding proteins Chordin (Chd), and Noggin (Nog) a mathematical model was developed and optimized against the population data for wild type and Chd mutants. The results of the data-driven computational model were presented.

Mechanical coupling coordinates the co-elongation of axial and paraxial tissues

Fengzhu Xiong (Harvard Medical School)

The embryonic body axis is composed of tissues that elongate at the same pace despite exhibiting strikingly different cellular organization. In this talk, Dr. Xiong provided evidence of

mechanical coupling coordinating the co-elongation of axial and paraxial tissues. Combining microsurgery and live-imaging in avian embryos, he showed that the presomitic mesoderm (PSM) compresses the neural tube (NT) and notochord (NC) medial-laterally promoting their convergence and elongation. Based on the computational simulation, he showed that cell motility in the PSM exerts a lateral-medial compression on axial tissues, which was further tested experimentally. Surprisingly, this axial push in turn is required for promoting addition of new cells to the PSM. Such interactions form a mechanical positive feedback loop that couples elongation of paraxial and axial tissues. In addition to experiments, Dr. Xiong used a cell based model with a cell motility gradient in PSM to explain tissue and cell behaviors.

The feather as a platform for mathematical modeling

Cheng-Ming Chuong (University of Southern California)

The geometric forms and exquisite arrangement patterns of the feather provide a great opportunity for mathematical modeling. With feathers in the adult bird as the multi-scale platform, Dr. Chuong and his group have been collaborating with experts in mathematical modeling and have gained a deeper understand of morphogenesis. For instance, he talked about periodic patterning involving Turing principles, in which molecular analyses of hair follicle formation provide evidence to support the most well-known mathematical model for biological pattern formation. In addition, he discussed how collective cell behavior in developing skins that translate molecular signals into tissue patterns, modeling work on feather exhibiting distinct branching forms, a recent work on assembling an intra-dermal muscle network in a feather tract and adapting the network configuration in response to external stimuli, and so on.

Wednesday, March 8, 2017

Models of Cell Motility

Hans Othmer (University of Minnesota)

Dr. Othmer presented the modeling of cell motility where the area is particularly of interest in metastasis. Dictyostelium discoideum (Dicty) is an appropriate system to study since it is a simple organism but has various interesting modes of motility including gliding, swimming, and walking. The chemotactic response of Dicty in the fluid was expressed by its shape changes during the movement. Dr. Othmer classified three major problems to study motility of Dicty: the transduction problem, the interior problem, and the exterior problem, and he focused on the first and the last problems in the talk. In the transduction problem, they tried to understand how extracellular signals are transduced into intracellular signals that can be used to control the shape changes using the mathematical model for reaction-diffusion systems. In the exterior problem, they study how the shape changes give rise to motion, how fast they move, and how efficient the motion is using the mathematical model for Navier-Stokes' equation.

Getting in Shape: in vivo and in silico studies of tissue mechanics in growth control

Yanlan Mao (University College London)

Dr. Mao explained how tissue size and shape are controlled is a fundamental biological question that still remains remarkably ill understood. Using a combination of genetics, live imaging, experimental biophysics and computational modeling, Dr. Mao showed that tissue mechanical forces can have an instrumental role in controlling cell shape patterns and cell division orientations. Also, differential proliferation rates can generate global patterns of mechanical

tension to orient tissue growth in a self-perpetuating and self-organizing manner. These patterns of mechanical forces can also drive cytoskeletal rearrangements and 3D tissue morphogenesis.

Direct and dynamic lineage analysis in amniote embryos

Rusty Lansford (University of Southern California)

Dr. Lansford is studying embryo morphogenesis, the mechanisms behind it and how mistakes can happen. Using transgenic quail, they can dynamically image cells in morphogenesis to generate data for quantitative analysis. Using this data, they were able to identify heterogeneity in the population of cells. A question of interest for Dr. Lansford is to understand why there are different expression levels. It was found that cells with high expression are germinal crescent and migratory. To understand how these cells set apart from other cells in gastrulation, they used 4D microscopy and generated data that can be used to measure position, movement, speed and trajectory of different cells. This work can contribute to understanding cell behavior, proliferation, movement, organization and fate.

Tissue-level communication through patterning of intercellular calcium wave dynamics

Jeremy Zartman (University of Notre Dame)

As a second messenger that integrates information from multiple signaling pathways to the cell, calcium ions are a prime candidate for providing important information on both the overall mechanical state of the tissue and resulting behavior at the individual cell level during development. In this talk, Dr. Zartman used an established model system of an epithelial tissue, the *Drosophila* wing imaginal disc, to investigate how tissue properties impact the propagation of intercellular calcium waves (ICWs) induced by laser ablation. He developed a chip-based regulated environment for micro-organs (REM-Chip) that enables them to identify essential conditions for generating organ-scale ICWs. He demonstrated that the dynamics of spontaneous ICWs are regulated by morphogenetic signaling and that ICWs propagate information at the organ-scale that reflects the differentiation states of developing wing disc. Given that the morphogenetic signaling results in a secondary level of pattern formation that emerges in calcium waves, understanding how calcium dynamics encode morphogenetic information at the tissue scale provides insights into the development and have a broad range of potential medical applications.

Cellular morphogenesis in Silico

Troy Shinbrot (Rutgers University)

Cells can migrate (deterministically or stochastically), interact (attractively, repulsively, etc.), reproduce, die and change shape. In this talk, Dr. Shinbrot described an agent-based approach that simulates these cell activities. He started with applying this Silico approach to a 2D example of looking at the skin patterning in zebrafish, which enabled him to demonstrate that homotypic repulsion is needed for stripes-like patterning. Dr. Shinbrot also looked at 3D examples and obtained some expected patterns observed in experiments by varying homotypic and heterotypic strengths. However, he also discovered some previously unreported patterns. Furthermore, Dr. Shinbrot explained mathematically the mechanisms underlying the generation of patterns, which happen regularly under well-defined conditions.

In addition to cell migration and interaction, he also applied the Silico approach to simulate cell reproduction, differentiation and death. These simulations are performed on several examples

and he specifically discussed ductal carcinoma in situ that can form various structures and used modeling simulations of cellular growth to understand these structures and what do they tell us about the growth history of the cells. Examples on cell shape change are also introduced at the end.

Special seminar: on growth and form and mathematics: D'Arcy Thompson

Philip Maini (University of Oxford)

Dr. Maini presented this special seminar dedicated to the memory of D'Arcy Thompson and talked about how D'Arcy Thompson's work has greatly affected mathematical biology. D'Arcy Thompson was the author of the book "On Growth And Form", which was firstly published in 1917 and appeared in many different forms. One main idea of this book is that natural sciences need a mathematical foundation "as the astronomy of Newton and Laplace". Back to his time, people understood things in turns of evolution and people thought things exist and grow because of their functions. D'Arcy Thompson was one of the first people asking what is the mechanism that forms these functions, why are animals and plants the way they are? His focus was mainly on geometry and forces and the idea is creating a mathematical understanding of these. Dr. Maini talked about D'Arcy Thompson's ideas on the evolution of growth, scaling of growth and relative growth that different parts of the body grow at a different rate in order to understand development. In terms of the "Form", Dr. Maini talked about the power of analogies, the problems with analogies, the ideal shape, and some famous work on transformations done by D'Arcy Thompson. Finally, Dr. Maini talked about what Thompson did in mathematics, current challenges linking biochemistry to biomechanics, and exciting future opportunities.

Thursday, March 9, 2017

Cell biology processes: model building and validation using quantitative data

Ruth Baker (University of Oxford)

Dr. Baker first questioned how the quantitative data obtained to study tumor growth, embryo development and wound healing can help to understand cell biology processes such as cell motility, proliferation, apoptosis, and adhesion. Different models were already developed to help to understand these cell biology processes. Dr. Baker focused on exploring some of these models for the growth and invasion of cell populations. Predictions made by the models will significantly depend on the parameter values used, so she discussed how the statistical inference techniques could be applied to estimate their parameters in these models utilizing cell or population level quantitative data. Then, Dr. Baker introduced a simple lattice-based model with two parameters for proliferation and movement and showed how these two parameters could be estimated using the approximate Bayesian computation approach since the likelihood is intractable due to the high dimension of the data.

Period and pattern in the embryo

Andrew Oates (Ecole Polytechnique Federale de Lausanne)

Dr. Oates presented on the segmentation clock and their pattern formation. The segmentation clock is a multi-cellular system of genetic oscillators, and it is known to control the rhythmic and sequential formation of the body segments in the vertebrate embryo. Each oscillating individual cell synchronizes with its neighbors, and these cells form a wave pattern of the gene expression. Dr. Oates focused on clarifying how these waves arise and are regulated during the

embryogenesis. He described recent progress to understand the behavior of the individual cells when they slow their oscillations and differentiate during segmentation and the relationship between this behavior and the tissue-level wave patterns.

Mechanics of epithelial morphogenesis

Celeste Nelson (Princeton University)

Dr. Nelson focused on how the branches form during the lung development. In general, mechanical forces generated by the cell drive the tissue movement and rearrangements, but these forces do not necessarily arise from active cellular movement. Dr. Nelson reviewed the roles of the passive mechanical forces during the lung morphogenesis, which generate mechanical instability between epithelial tissues and their surroundings. This instability converts the one-dimensional epithelial tube to the complex-shaped lung branches. Their work suggested a new tissue development class such as buckling and wrinkling morphogenesis in the lung, and the study of the underlying mechanisms of instability can help to better understand the formation of the complex topologies in other organs.

Data-driven multiscale and stochastic modeling of cell fate dynamics in tissue growth

Qing Nie (University of California, Irvine)

In the tissue growth and morphogenesis, cell fate dynamics involve various scales and are affected by the noise significantly. In this talk, Dr. Nie presented multiscale and stochastic models to understand the spatial tissue dynamics, which can utilize single-cell molecular data. Using the suggested models and related experimental data, Dr. Nie showed how the binding proteins, feedback loops and noise in cell plasticity or cell to cell sorting can help to generate spatial patterns in the tissue and how these factors can increase the robustness in the pattern formation. His work showed how to link the underlying networks in the tissue growth and the various models in optimization, differential equations, stochastic processes and machine learning by utilizing experimental data.

Friday, March 10, 2017

Molecular and mechanical mechanisms of tissue size control

Sean Megason (Harvard Medical School)

Dr. Megason's lab combines in toto imaging in zebrafish embryos, with mathematical modeling, and molecular and mechanical perturbations to try to understand how groups of cells work together to form patterns and shapes. Dr. Megason discussed recent stories in the lab focused on understanding how tissue/organ size is controlled. In the inner ear they found that size is primarily controlled by negative feedback between flux of fluid into the otic vesicle and hydrostatic pressure. For somites, they found that size is controlled by scaling of a molecular gradient. In the neural tube they found that size is controlled based on mechanical feedback on differentiation rate.

Vertex models of epithelial morphogenesis

Alex Fletcher (University of Sheffield)

Dr. Fletcher explained how embryonic epithelia achieve complex morphogenetic movements through the coordinated action and rearrangement of individual cells. In combination with experimental approaches, Dr. Fletcher showed how computational modeling can provide insight

into these processes. Dr. Fletcher described applications of vertex models, a widely-used class of computational model for epithelia, to investigate the role of patterned cell mechanics in two settings in the *Drosophila* embryo: tissue size control and convergent extension. Biological insights gained through this work were highlighted and Dr. Fletcher also presented some recent extensions to 3D morphogenesis.

Spring Workshop 3: Hybrid Multi-Scale Modelling and Validation **(March 27 - 31, 2017)**

Organizers: Tomas Alarcon (Centre de Recerca Matematica), Helen Byrne (University of Oxford), James Glazier (Indiana University)

Report by: Jeff Gaither, Nesy Tania, Casper Woroszylo

MONDAY MARCH 27, 2017

A mathematical model of the Hippo growth control pathway in developing tissues

Hans Othmer (University of Minnesota)

Dr. Othmer discussed the Hippo pathway and its role in the control of cell proliferation and apoptosis in *Drosophila* and mammalian cells. Specifically, the Hippo pathway contains a core kinase mechanism that affects control of the cell cycle and growth. Dr. Othmer introduced a mathematical model, based on partial differential equations, that incorporates the current understanding of the Hippo signal transduction network in wing disc formation for *Drosophila*. The model qualitatively explains both the observations on whole-disc manipulations and the results arising from mutant clones. Variance-based sensitivity analyses were performed to determine which parameters were influential in the underlying mathematical model. Dr. Othmer found that a number of non-intuitive experimental results can be explained by subtle changes in the balances between inputs to the Hippo pathway. Since signal transduction and growth control pathways are highly conserved across species and directly involved in tumor growth, much of what is learned about *Drosophila* will have relevance to growth control in mammalian systems.

Up-close and personal with drug delivery: the medical imaging-informed hybrid models of micro-pharmacodynamics

Katarzyna Rejniak (H. Lee Moffitt Cancer Center)

Classical models of pharmacokinetics and pharmacodynamics (PK/PD) represent tissues and organs as homogeneous well mixed compartments. However, both normal and tumor tissues are heterogeneous in their structure and response to metabolites and treatments. Dr. Rejniak presented a novel in silico microPK/PD model of drug pharmacokinetics and pharmacodynamics on the microscopic cell-to-tissue scale that enables tracking of drug efficacy within the tissue on the level of individual cells. Medical imaging techniques, such as immunohistochemical staining, bright field microscopy and confocal fluorescent imaging, informed and calibrated the models. In particular, properties of tumor cells, cell colonies and tumor microenvironment were incorporated into the model. This allowed for examining the drug intratumoral distribution in the in silico-reconstructed tumor organoids. Such a method can be used to build a predictor of tumor chemoresistance based on clinical biopsies routinely collected for cancer diagnosis. The use of data from individual patients' tumors hold promise for designing personalized treatments.

From single models to community advances: open source codes and data standards

Paul Macklin (Indiana University)

Understanding of complex diseases such as cancer requires knowledge on how tissues self-organize many processes such as division, differentiation, intercellular communication, angiogenesis, etc. Past modeling efforts tend to focus on one aspect only. Part of the bottleneck is that it usually requires a huge investment of time and efforts to build computational tools that can tackle even just one specific aspect. Dr. Macklin proposed building 3D simulation frameworks that include modular subsystems, allow for connection to data (for parameter estimation), and are open-sourced and reproducible. Thus, the efforts can be shared and developed within a larger community leveraging the expertise of different groups. Dr. Macklin presented three such ongoing efforts from his team. (1) BioFVM is a 3D simulation platform for biotransport of many chemicals. It is developed for efficiency by splitting 3D diffusion into coupled 1D diffusion problems. Solving the transport is akin to setting the “stage” if we think of the bigger problem as a theatrical play. (2) PhysicCells is an agent based simulator that allows for tracking of millions of cells on a single desktop. This tool allows for the “actors” to be specified. (3) CellPH is a cell-line phenotype digitizer for parameter estimation. Parameter determination gives the “script” for the developmental biology (or cancer) play. Dr. Macklin closed his talk by inviting the community to utilize and contribute to the development of these tools.

Heterogeneous quiescence exit displays a memory of preceding cell cycle position and division

Guang Yao (University of Arizona)

Cell quiescence is a reversible non-proliferative state typically associated with G0 in the cell cycle. The reactivation of quiescent cells upon growth stimulation is critical to tissue repair and homeostasis. The quiescence-exit process is highly noisy even for genetically identical cells under the same environmental conditions with poor understanding for why such heterogeneity exists. To determine the source of heterogeneity, Dr. Yao used modeling in tandem with experiments to compare measurements and perturbations in the distribution of a population of quiescent cells in their responses to growth signals. He found that quiescent cells display a memory of their preceding cell cycle positions and division histories. Dr. Yao also showed that the deterministic positional memory of quiescent cells, coupled with the stochastic dynamics of an Rb-E2F bistable switch, jointly and quantitatively defined the heterogeneous exit from cellular quiescence.

The relationship between cell and tissue dynamics in healthy and precancerous epithelium

Inke Nathke (University of Dundee)

The crypts of the intestinal epithelium house the stem cells that ensure the continual renewal of the epithelial cells that line the intestinal tract. Crypt number increases by a process called crypt fission, the division of a single crypt into two daughter crypts. Fission drives normal tissue growth and maintenance. Correspondingly, it becomes less frequent in adulthood. Importantly, fission is reactivated to drive adenoma growth. The mechanisms governing fission are poorly understood. However, only by knowing how normal fission operates can cancer-associated changes be elucidated. We studied normal fission in tissue in three dimensions using high-resolution imaging and used intestinal organoids to identify underlying mechanisms. Dr. Nathke discovered that both the number and relative position of Paneth cells and Lgr5+ cells are important for fission. Furthermore, the higher stiffness and increased adhesion of Paneth cells are involved in

determining the site of fission. Formation of a cluster of Lgr5⁺ cells between at least two Paneth-cell-rich domains establishes the site for the upward invagination that initiates fission.

TUESDAY MARCH 28, 2017

Coupled multiscale modeling and pathway analysis for prediction of drug efficacy in cystic kidney diseases

James Glazier (Indiana University)

Extensive research has uncovered many genetic changes associated with autosomal dominant polycystic kidney disease (ADPKD) and effects of ADPKD mutations on signaling pathways. However, the precise sequence of events that lead to cyst initiation remain unknown. One of the key changes during the initiation of cysts is abnormal expression of the juvenile cell adhesion molecule cadherin-8. Dr. Glazier examined two hypothetical cell-level mechanisms by which abnormal expression of cadherin-8 could initiate cyst formation: i) reduction of cell-cell adhesion, which then leads to changes in cell proliferation or ii) direct reduction of contact inhibition of proliferation with no change in cell-cell adhesion. To test these mechanisms, Dr. Glazier developed a 3D virtual-tissue (VT) computer model of the renal tubule using the CompuCell3D (CC3D) modeling environment showing that loss of adhesion mechanism produced morphologies matching in vitro cadherin-8 induced cysts. Concurrently, Dr. Glazier used the Transcriptogram method for whole-genome gene expression analysis to analyze microarray data from cell lines developed from cell isolates from normal kidney and from both non-cystic nephrons and cysts from the kidney of a patient with ADPKD. We identified novel pathways altered in ADPKD. Transcriptogram significance metrics identified increased expression of cGMP phosphodiesterases as the highest priority pathways for study. Dr. Glazier's modeling and experimental efforts then focused on cGMP phosphodiesterase inhibitors, a class of drugs already FDA approved for other uses. Using pathway analysis, Dr. Glazier linked the cell behaviors known to drive cyst formation with increased cGMP phosphodiesterase expression and constructed models of these pathways using Cell Designer. Preliminary in vitro and mouse model testing of phosphodiesterase inhibitors to reduce cyst formation have shown efficacy.

Investigating growth within curved layers of cells using the Cellular Potts Model

John Fozard (John Innes Centre)

The cellular Potts model (CPM) has been applied to investigate the behaviours of many different multicellular tissues. For some plant tissues, such as leaves and the shoot apical meristem, a single curved layer of cells is of primary interest. Assuming this curved layer can be represented by a triangulated surface, Dr. Fozard considered the formulation of the CPM on such an irregular, non-uniform lattice. Such a formulation is then used to apply segmentation methods, based upon the CPM, to quantify geometric properties of cells within curved layers of cells, using data from confocal microscopy images. Dr. Fozard further explored coupling cell-scale models to coarser discretizations of organ shape, and used these to explore plant organ growth and development. In particular, he used the model to inform finite-element based models for bladder growth.

A step towards virtual experiments in organ micro-architectures: growth factor signaling, ammonia detoxification and drug metabolism in a virtual liver lobule

Dirk Drasdo (Institut National de Recherche en Informatique Automatique)

As a step towards a virtual liver lobule, Dr. Drasdo showed how a stepwise a multilevel model of drug-induced damage, regeneration and the detoxification of ammonia during regeneration is developed. In particular, Dr. Drasdo showed how the iterative application of a pipeline consisting of confocal scanning microscopy, image analysis and modeling can be used to design a predictive model of tissue regeneration and metabolism suited to guide modeling driven experimental strategies. In the case of hyperammonemia such a strategy has led to the model-guided identification of a so far unrecognized mechanism in ammonia detoxification that has the potential to improve therapy. While the former works based on an integrative model, that links a compartment model of ammonia detoxification with a spatial-temporal micro-architectural agent-based model of liver regeneration after drug induced liver damage, Dr. Drasdo compared the integrated model with a full multi-scale, multi-level model whereby the detoxification reactions are executed in each individual hepatocyte, and discuss critical differences. Finally, Dr. Drasdo extended the multiscale model by integrating a model of toxic damage by acetaminophen in each hepatocyte, as well as hgf induced cell progression during the regeneration of tissue damage caused by acetaminophen.

Agent-based modeling of cells in tissues to understand and predict disease

Shayn Peirce-Cottler (University of Virginia)

The most prevalent, devastating, and complex diseases of our time, such as diabetes, cardiovascular disease, and infectious diseases, result from the interactions of heterogeneous cells with one another and with their environment. However, the emergence of disease from these interactions at the multi-cell level is still poorly understood, and drugs typically target single molecular pathways while disregarding how cellular heterogeneities might affect drug efficacy at the tissue-level. To address this void, Dr. Peirce-Cottler developed new computational tools in combination with experimental approaches in order to integrate and predict how individual cell behaviors dynamically give rise to physiological and pathological tissue-level adaptations. Leveraging the versatility and adaptability of agent-based modeling, Dr. Peirce-Cottler simulated structural adaptations of large and small blood vessels, skeletal muscle regeneration following injury, and immune cell trafficking and differentiation during inflammation and infection. These studies have suggested new mechanistic hypotheses and provided guidance for the design of novel therapies. In particular, these models rule false hypotheses out; integrate information and experiments from many sources; implement hypotheses and run in a controlled virtual environment. Quantitative predictions may need to represent spatial micro-environment.

Quantitative Methods for High-Throughput Live Cell Imaging

Jens Rittscher (University of Oxford)

This talk discussed the recent developments in the imaging of live cells, a practice that is becoming more and more viable and useful as technology improves. It is now possible to actually observe cells, and their interactions with each other, in a very meaningful sense. Modern methods of live cell imaging rely heavily on machine learning. One particularly exciting development is the 3D culture, a method which approximates an *in vivo* environment to a degree not hitherto attained. Dr. Rittscher also discussed some active areas in his current research, which include studies on the interaction of population of epithelial cells and on the evolution of organoid cell cultures.

Hybrid multi-scale modelling of angiogenesis

Timothy Secomb (University of Arizona)

Dr. Secomb presented a new multi-scale model for the phenomenon of angiogenesis, which is the process by which new blood vessels are grown. In contrast to a single-scale model, which would typically use a network in which the edges are vessels and the nodes are the divergence-points, the speaker's paradigm also considers the effects of individual cells pushing against the walls of existing vessels, which is the actual mechanism by which angiogenesis is achieved. The mathematics for this model take into account certain factors in the surrounding micro-environment, such as oxygen concentration, which have undeniable biological bearing on this process, and solve the resulting reaction-diffusion equations using a numerical method that relies conceptually on the idea of Green's function. A multi-scale model seems to have proven necessary for modeling angiogenesis, and the use of such models to model micro-interactions is perhaps an idea that is rising in currency.

WEDNESDAY MARCH 29, 2017

Tumor Microcirculation, Vascular Targeting and Biomarkers: insight from pre-clinical models

Gillian Tozer (University of Sheffield)

Dr. Tozer discussed the state of the art in the field of angiogenic cancer treatment, whose goal is to obstruct the spread of cancer into new blood-vessels and more generally into the process of blood-vessel making, which is called angiogenesis. The canonical way of carrying out such a treatment is via the vascular endothelial growth factor, or VEGFA, which was clinically approved in 2004. The speaker revealed that clinical trial experiments are underway for certain tumor vascular disruptive agents, or VDAs, whose designed purpose is to disrupt a tumor's usurpation of healthy blood vessels. A challenge is that no reliable biomarker exists for the usefulness of anti-angiogenic treatment in a given patient. But there is strong reason to believe that the clinical trials currently underway will shed some light in this direction.

Cellular behaviours underlying tissue dynamics during primitive streak formation in the chick embryo

Cornelis Weijer (University of Dundee)

Traces of individual cell velocities during gastrulation in chick embryos reveal a vortex flow, when viewed on a larger embryo scale; the flow is similar to Stokes flow with two counter-rotating vortices in circular domain. Dr. Weijer asked what cell behavior generate forces for such coordinated flow? Using light sheet microscopy, his lab was able to track movements and behaviors of over 200,000 cells. At an individual level, cells divide or ingress to a deeper layer (forming sources or sink) as well as intercalates with one another (contraction and expansion). These generate large scale deformation that are primarily driven by pulling rather than pushing forces. These forces are generated by myosin light chain; in fact, actin and myosin form cable patterns within the tissue and inhibition of myosin II lead to a block in streak formation.

Dr. Weijer also presented several ongoing work to further tease apart processes in primitive streak formation. One was to measure junctional tension by using optical tweezer. The second was to solve an inverse Stokes flow problem – find the force that best describe the experimental velocity profile. The third is the development of active vertex model where elements (cell centers) are treated as an active particle and the effects of myosin-actin are implemented as a catch bond (pulling leads to stronger bonds) and tension allow formation of myosin cable. The model provides

a platform for studying how local interaction at the cell-cell level leads to long range force generation at the tissue level.

Hybrid Multiscale modelling for the design of a virtual tumour

Angélique Stéphanou (Laboratoire TIMC-IMAG / UMR 5525, CNRS)

Virtual tumors are a natural tool for cancer treatment which have only recently become computationally possible. The underlying logic for a virtual tumor is to gather as much useful data about the patient as possible, and then simulate the tumor's growth and (very importantly) response to treatment. In principle this is a wonderful idea, but there are many factors at play in a tumor's progression, and Dr. Stéphanou has developed a model for tumor kinetics which addresses angiogenesis, matrix remodeling, hypoxia and cell heterogeneity. This approach has been developed from a preclinical mouse model, and relies on fluorescence imaging.

Multi-scalar modelling of the microvasculature: how do biologists and modellers get it less wrong?

Christopher Mitchell (Ulster University)

Dr. Mitchell discussed the role and importance of the microvasculature, which is a term for the system of capillaries, the smallest blood vessels, throughout the body. Many studies have shown that the capillaries located near given organs are adapted to most efficiently supply those organs with blood. The great difficulty with modelling capillaries is that they form a vast system in which numerous factors operate upon these vessels which are extremely small and numerous. Cross-disciplinary understanding is extremely important, since both biological understanding and mathematical modeling of the microvasculature required considerable effort.

Cancer Biology, a Systems Biology View

Aviv Bergman (Albert Einstein College of Medicine)

Dr. Bergman presented his work in combining evolutionary modeling and classical cell-based mathematical modeling to understand cancer progression. From a disciplinary tradition, the field of molecular and cell biology embraces complexity while avoiding the question of variation; meanwhile, evolutionary biology prefers simplicity but emphasizes understandings for mechanisms that lead to variations. Natural selection favors genetic mechanisms that would buffer variations leading to robustness of characters/phenotypes. Dr. Bergman presented an in-silico model of network transcription which consists of a dynamic map (Markov chain) between genome to gene product found that perturbations (knock out experiments, mutations, etc.) to the matrix representing gene network led to a wider variations in the steady-state fate of the gene product (phenotypes). Based on this, Bergman then asked if cancer (akin to knockout or gene mutation) then lead to a wider phenotype at the cellular level. He explored this question in three settings. First by looking at tumor vs. normal genome wide expressions, 108 genes were found to be expressed in higher variations amongst high risk patients. Second, in the context of metastasis, his team compared gene expressions of cells that migrate v.s. those that stay in the primary tumor when exposed to a growth factor. They identified two class of genes, an upstream regulator TGFB1 that appeared to be stable (i.e. consistently up/down regulated) and another class HGF genes that have a wide range of expressions in metastatic cells. Third, Bergman also studied how tumor microenvironment are associated with two tumor cell motility phenotypes (slow vs fast migrators).

Dr. Bergman also discussed the dilemma of robustness: how can multicellular organism maintain robustness while also respond (exhibit different phenotypes) to environmental cues? There are two types of robustness: mutational robustness and environmental robustness. For single cell organism, both modes of robustness are tightly coupled. However, for multicellular organism, there must be a sensitivity during development that allow cells to differentiate in response to its environment. The two robustness modes are decoupled. A control mechanism allows for cells to commit to a particular gene network depending on its variations. This then allow for variation while also maintaining robustness. In the context of cancer, Dr. Bergman then proposed that this ability to commit is broken so that cancer cells can switch between different phenotypes depending on its environment

Yi Jiang (no talk)

THURSDAY MARCH 30, 2017

Model for the early development of meristems

Rafael Barrio (Universidad Nacional Autonoma de Mexico)

Stem cells are *tabula rosa* cells that can be modified by the body into the worker-cells that comprise a human being. It follows, somewhat obviously but nonetheless interestingly, that stem cells must interact with surrounding tissue if they are to grow into functional cells. Dr. Barrio discussed some possible chemical or physical-field-based phenomena by which the crucial spatial interactions of stem cells might take place. His study focused on the root apical meristem of *Arabidopsis thaliana*, and endeavored to identify cellular patterns that physically appeared. He also presented a model to study the dynamics of the divisions of cells with auxin concentration and physical elastic fields.

Long and short time-scale rheology of living cell monolayers

Guillaume Charras (University of College London)

Dr. Charras discussed responses of cell monolayer to stretching/compression at different timescales. One-cell thick monolayers are the simplest tissues in multi-cellular organisms, yet they fulfill critical mechanical roles in development and normal physiology. For examples, alveola in the lung consist of monolayers and are exposed to high shear; during development, a single layer can exert forces on the entire tissue. To study their properties, the Charras lab uses a setup consisting of a cell monolayer that are freely-suspended by two rods. In stress-relaxation experiments, they found that the response is biphasic. At a short time-scales, relaxation followed a power law behavior, but at a longer time-scale (minutes), the relaxation was ATP-dependent with myosin conferring a solid-like behavior to the monolayer. Dr. Charras also discussed responses at a much longer timescale of hours. Prolonged stretching led to oriented cell divisions where divisions were oriented by shape (stretching elongates cell in direction of the stretch axis) rather than stress. This emergent oriented-divisions drove relaxation of tissue and the return to resting cell packing.

Identifying and modeling contractile trans-tissue structures in morphogenesis

Guy Blanchard (University of Cambridge)

A lot is known about gene expression and gross tissue shape changes during development. Mechanics mediate the two processes, but is less understood. Dr. Blanchard presented his work in the development of computational and image analysis tools to study movements during the

development of *Drosophila* embryo. Imaging datasets were first used to track individual cells in terms of their trajectories and shape changes over time. These discrete cell behaviors were then used to determine a viscoelastic stress strain relationship, which can be broken down into translation, dilation, rotation, etc. Fluorescence intensity data for myosin was also quantified to determine contractility in cell-cell junction and tissue. These results were then used to inform parameter estimates for a vertex-based computational model. The model, which took into account cell elasticity, cortical contraction, and line tension, was used to determine essential components for extension and convergence observed during the development in *Drosophila* embryo.

The impact of collecting data at varying temporal resolution on parameter inference for biological transport models

Jonathan Harrison (University of Oxford)

Experimental data are collected at discrete time points, and the resolution at which data are collected can introduce error when motion is approximated as a single step from one time point to the next. Dr. Harrison discussed how data collection at different temporal resolution can influence parameter inference for biological transport models. More specifically, a velocity jump model was considered and estimates of turning rate and noise amplitude can be obtained in a Bayesian framework. These estimates were sensitive to the temporal resolution of the data and noise. As a take-home message, they suggested that for imaging experiments, better parameter estimation can be obtained by taking data more frequently even if this leads to noisier data (fixed photon budget).

A modeling and simulation environment for biological cells with coupled mechanical and chemical processes

Endre Somogyi (Indiana University)

Dr. Somogyi presented the Mechanica modeling language, a coding framework specifically designed for the mechanistic modeling of physical phenomena. He first gave a survey of the problems inherent in modeling and simulating the actual mechanics of cells in an *in vivo* environment. He presented the multicellular mechanical relations of Satoru Okuda, and expressed the opinion that classical molecular dynamics is inadequate for large-scale cellular dynamical systems. He also pointed out that a large problem with creating new approaches is that they are usually custom-coded by graduate students, which is not ideal since custom-coding is time-consuming and typically no one takes an interest in the code except the student himself/herself. It would, therefore, be helpful to all concerned if such code was written under a common framework which made it easier to share among scientists.

Roeland Merks (talk canceled due to family emergency)

FRIDAY MARCH 31, 2016

Mechanically-coupled Reaction-Diffusion model of Glioma Growth

Philippe Buchler (Bern University)

Gliomas are the most frequent brain tumors observed and represent a serious medical condition. The most malignant form of glioma show rapid growth and high density leading to compression and displacement of the surrounding tissue. Treatment to this increase in intra-cranial pressure often fails when the tumor reaches a critical size. Dr. Buchler presented his work in quantifying

the dependence of morphology and mechanical tumor characteristic on their growth location using simulation of mechanically-coupled reach diffusion system for glioma growth.

Organization of vascular pattern in plant roots

John King - Organization of vascular pattern in plant roots

In more complex plants, two important players in the metabolic process are the xylem vessels, which distribute nutrients and water from the roots to the shoots, and the phloem, which transport the photosynthetic products generated in the plant's shoots into the roots. Dr. King focused much of his attention on the genus *Arabidopsis*, a kind of mustard plant in which each root has exactly two xylem vessels and two phloem vessels in every root. Some mathematical modeling has demonstrate that under the models, an assymetry in the hormone auxin may set down the vascular pattern before the seed is germinated. The author also pointed to some conspicuous questions in this field, such as how the vascular pattern roots can be altered by experimental manipulation.

Spring Workshop 4. Women Advancing Mathematical Biology: Understanding Complex Biological Systems with Mathematics

April 24 - 28, 2017

Organizers: Rebecca Segal (Virginia Commonwealth University), Ami Radunskaya (Pomona College), and Blerta Shtylla (Pomona College)

Report by: Reginald McGee, Farrah Sadre-Marandi, and Leili Shahriyari

Description

This workshop has a special format designed to create and support six high quality research collaborations between senior female researchers working in mathematical biology and junior mathematicians. Each group will be led by a senior research mentor and a junior co-leader. Additional team members are chosen from applicants and invitees. The groups spent a week making significant progress with their research project and fostered innovation in the application of mathematical, statistical, and computational methods in the resolution of problems in the biosciences. In addition to modeling goals, the aim is to provide women in mathematical biology with an opportunity to be more inclusive to their peers and provide avenues for positive professional growth and development for all participants.

This workshop was a starting point for these research collaborations. It is expected that each group will continue to work on their project together after the workshop. Results from the workshop will be published in a peer-reviewed volume, highlighting the contributions of the newly-formed collaborative groups.

MONDAY, APRIL 24, 2017

Project Introductions

PROJECT 1: *Stochastic Modeling of Infectious Diseases: Heterogeneity of Hosts and Pathogens*

Leader: Linda Allen (Texas Tech University)
Co-Leader: Angela Peace (Texas Tech University)

Models formulated to study intervention, prevention, and control of an emerging disease should consider pathogen virulence, host susceptibility and transmissibility, population features. Individual characteristics determine susceptibility and transmissibility history of exposure, genetic predisposition, physical health, etc. The importance of host heterogeneity in disease emergence has been demonstrated in historical and in recent epidemics that involve super-spreaders. Super-spreading occurs when a single patient infects a disproportionate number of contacts. The project aims to investigate different sources of heterogeneity (e.g., pathogen virulence, host susceptibility, host transmissibility, host behavior, mixing patterns, environment, etc.) that impact the probability of a major epidemic. To reach this aim, they use more detailed, time-dependent stochastic models and methods, continuous-time Markov chains, stochastic differential equations, continuous-time branching processes, and numerical simulations.

PROJECT 2: *Explaining Autism Spectrum Disorder with Placenta*

Leader: Jen-Mei Chang (California State University, Long Beach)
Co-Leader: Kellie Archer (Ohio State University) and Karamatou Djima (Amherst College)

Recent medical research indicates that the placenta may be the “crystal ball” for the health of the newborns since placenta is the source of nutrition, oxygen, and blood for the developing fetus. Problems with the placenta may manifest as developmental issues for the baby. Newborns at high-risk for autism spectrum disorder (ASP) have a vascular network in their placenta that is structurally different than newborns at low-risk for ASP. For example, they differ in the number of branching points and vessel thickness. Though the placental chorionic surface vascular network has not been extensively studied due to the extreme difficulties in reliably extracting its features from digital images of the fetal surface. This project will explore mathematical models used to extract data from 3D images to see whether differences in high-risk ASD placentas are confined to children actually diagnosed with ASD at 3 years of age, or whether high-risk families have global and basic differences in placental morphology.

PROJECT 3: *Ectoparasites and Allogrooming - Evolutionary Trade-offs in Animal Community Health*

Leader: Nina Fefferman (University of Tennessee, Knoxville)
Co-Leader Shelby Wilson (Morehouse College)

Evolution along the social continuum means that individual fitness is more dependent on others and individuals are more at risk from each other for instance infectious disease and indirect loss of individual fitness if “others fail”. Disease is *usually* considered in the literature as a constraint operating against increasing sociality. The goal of this project is to Figure out what all this means for parasitic infections. Parasites involve three big differences from infectious pathogens. Grooming removes parasites from others, but exposes the groomer to infestation. Additionally, infestation isn’t Boolean (as the infectious disease case was), so the parasite load is important to health outcomes for the host and re-exposure of an already infected individual can increase load. Evolutionary outcomes first affect reproduction, then affect survival.

PROJECT 4: *Modeling Argasid Ticks*

Leader: Holly Gaff (Old Dominion University)

Co-Leader: Gaby Hamerlinck (Bioquest)

Tick families include Ixodid (hard ticks) and Argasid (Soft ticks). Soft ticks can be found in nesting and resting areas. One of the characteristics of soft ticks is rapid feeding (1 hr). The average lifetime of soft ticks is 5-12 years. Some species can live up to 20 years. The project aims to model soft ticks because of increased incidence of tick-borne disease, and there are no published model for soft ticks.

PROJECT 5: *Mechanics of Super-Fast Nematocyst Firing*

Leader: Laura Miller (University of North Carolina at Chapel Hill)

Co-Leader: Wanda Strychalski (Case Western University)

Nematocysts are specialized cells containing a barbed or venomous coiled thread that can be projected in self-defense or to capture prey. Nematocysts, which are one of the least studied organelles, are super fast, largest accelerations in organisms. Nematocysts are specialized cells in the tentacles of a jellyfish or other coelenterate, containing a barbed or venomous coiled thread that can be projected in self-defense or to capture prey. The aim of this project is to model the movement nematocysts and test two hypotheses: 1) Puncturing requires getting to inertial regime and 2) Contracting walls increase pressure to force barb out of cell. The model is based on numerically solving the Navier Stokes equations with an added Eulerian elastic body force density with respect to the Eulerian coordinate system. Fluid-structure coupling is done via integral transforms with delta function kernels.

PROJECT 6: *Disease and Combination Therapy Dynamics*

Leader: Helen Moore (Bristol-Myers Squibb)

Co-Leader: Nissy Tania (Smith College)

In multiple myeloma (MM), both red blood cells and white blood cells do not function well. There is no cure for multiple myeloma, and median survival time is around 5 years. Current therapies can extend survival is more than 5 years. There are many therapies for MM – too many to test all combinations.

The goal of this project is to optimize multiple Myeloma Regimen. In this project, they use the draft model provided by Bristol-Myers Squibb to perform as much of the necessary theoretical analysis as possible. The model includes multiple myeloma cells, natural killer cells, effector T-cells, regulatory T-cells, and the therapies are pomalidomid, dexamethasone, daratumumab, elotuzumab, and nivolumab.

FRIDAY, APRIL 28, 2017

Project Summaries**PROJECT 1: *Stochastic Modeling of Infectious Disease Heterogeneity of Hosts***

This project aims to assess the importance of superspreaders on infectious disease dynamics and

make public health implications to help minimize the epidemic. A model was developed that incorporates the heterogeneity of hosts to capture the roles of superspreaders in an epidemic. The initial size of the superspreaders and model parameters were varied to predict the probability of an extinction and epidemic. Estimated parameter values from prior MERS-CoV and Ebola epidemics were incorporated and examined. Future work includes analyzing the difference in population to classify and identify potential superspreaders early in an outbreak to reduce the severity of infectious disease spread.

PROJECT 2: *Explaining Autism Spectrum Disorder with Placenta*

It is unknown how structural differences in the vascular network impact the network's function and whether any changes in function would also be associated with autism spectrum disorder (ASP). This project hypothesizes that the connection between structure and ASP is actually mediated by functional changes in how well oxygen can be delivered from the maternal heart to umbilical cord. First the statistical properties of the vascular network are traced by trained experts in two-dimensional space for both individuals at high-risk for ASP and individuals at low-risk for ASP. The branching networks are then simulated with similar characteristics to individuals at high-risk for ASP and individuals at low-risk for ASP, e.g., branching angles and branch thickness. These networks can be used to investigate potential mechanisms for the formation of patterns that have been observed empirically. Lastly, the simulated networks are used to evaluate the transport of oxygen to the umbilical cord. The transport combines an advection-diffusion model of oxygen through the placenta to the network with a model of the pressure and flow of oxygen through the network. The outcome is a way to estimate how well the vascular network can transport oxygen to the umbilical cord from its structure and can be used to predict individuals at risk for autism. In addition, this work highlights which features of the network contribute most strongly to its ability to transport of oxygen.

PROJECT 3: *Ectoparasites and Allogrooming - Evolutionary Trade-offs in Animal Community Health*

The motivation for this project was understanding evolutionary dynamics of social systems under parasitic constraints. The social actions taken by individuals in a network can lead to different levels of evolutionary success for the network, but these same actions can lead to success of a pathogen or parasite afflicting the population. This project aimed to explore the question: How do social network dynamics and parasite dynamics impact one another. Agent based simulations and continuous different equations were used to attempt to answer this question. After the random introduction of parasites, which possessed their own birth death dynamics, several agent-based simulations simulations where the network was allowed to converge randomly and according to three centrality metrics were compared. To measure population parasite burden two parameters were varied in the model: the rate of parasite reproduction and the efficiency of grooming. To formulate the continuous model mass-action kinetics were used. At certain parameter values, there were non-monotonic steady states which were also present in the agent based simulations. This phenomena is planned to be investigated in the future.

PROJECT 4: *Modeling Argasid Ticks*

Soft ticks are poorly studied compared to hard ticks and this was a motivation for the project. Moreover, there is agricultural importance in understanding the dynamics of how they transfer African Swine Fever Virus to warthogs and, ultimately, to domestic pigs due. There are

mathematical models for hard ticks in the literature but none for soft ticks. This project sought to use discrete and continuous modeling approaches to build a framework for understanding soft tick life cycle. The discrete model was simulated to track the total number of ticks when one of or both a small and large hosts was present. The model predicts that there will be the most ticks when there are both small and large hosts available; this agrees with biological intuition as ticks in different stages of life prefer hosts of different sizes. A partial rank correlation analysis was used to determine which parameters would most helpful in refining the discrete model. The continuous model used a Lotka-Volterra formulation and it was found that conclusions from the simulations agreed with those in the discrete case. Future work includes completing model analysis on the current model and comparing results between the two approaches, extend the models to include African Swine Fever Virus, and predict potential control measures for the virus.

PROJECT 5: *Super-Fast Firing of Nematocysts*

Nematocysts are specialized cells employed by Cnidarians (hydra, jellyfish, corals) and dinoflagellates that sting. Morphogenesis of these organelles are mostly understood but the firing of their venomous threads happens so fast, it is hard to be captured and analyzed. It is hypothesized that the explosive acceleration of the nematocysts allows the stylet to hit the prey, overcoming the interaction between stylet, fluid, and prey. This project aimed to simulate the fluid-structure interaction and explore how small changes in speed and shape can affect the local flow field. The starting model assumes that the rod will not touch the prey. Simulations were used to test the following three hypothesis: (1) it is easier to hit a big prey, (2) it is easier to hit a shorter distance, (3) it is easier to hit a more stiff prey. Future work includes testing if the nematocysts are ejected from the cell via applied force or pressure, studying the mechanics of how the capsule is triggered, and improving the elastic model for the prey.

PROJECT 6: *Disease and Combination Therapy Dynamics*

This project was aimed at finalizing a model for multiple myeloma to use in an optimal control framework to predict cancer drug therapies. The initial model was semi-mechanistic system of ordinary differential equations developed at Bristol-Meyers Squibb. To help determine the final structure the identifiability tableaus of model parameters was considered. Equilibrium analysis was used to investigate the number of possible steady states and ultimately identify parameter conditions that guarantee stable positive immune cell populations. Parameter values that couldn't be found in the literature were tuned as best as possible. The model was able to produce simulations for treatments with the drugs Elotuzumab and Nivolumab and their combination. Future work for this project includes finalizing model structure, bifurcation analysis, and proving the existence and uniqueness of solutions before the model can be used in an active intervention in a human population.

EDUCATIONAL PROGRAMS

Joint 2017 MBI-NIMBioS-CAMBAM Summer Graduate Program

Connecting Biological Data with Mathematical Models

[NIMBioS - University of Tennessee, Knoxville – Organized the Program]

(June 19-23, 2017)

Organizers: Janet Best (The Ohio State University); Anmar Khadra (McGill University); Suzanne Lenhart (University of Tennessee, Knoxville); Greg Wiggins (NIMBioS); Joseph Tien (The Ohio State University)

The MBI co-sponsored the Joint 2017 MBI-NIMBioS-CAMBAM Summer Graduate Program Connecting Biological Data with Mathematical Models

Location: NIMBioS, Claxton Bldg., on the campus of the University of Tennessee, Knoxville

This graduate program consisted of instructors from across North America whose research expertise is mathematical modeling in biological systems using real data. Some of the techniques covered include:

- Maximum likelihood and Bayesian approaches to inference
- Parameter estimation
- Model identifiability
- Uncertainty and sensitivity analysis

The program included lectures on techniques and modeling using specific data sets, and computer activities focusing on learning techniques and sessions to receive feedback on participants' own research problems. Researchers from the mathematical and biological sciences were featured speakers.

Speakers included:

Ben Bolker (McMaster University)
Ariel Cintron-Arias (East Tennessee State University)
Marisa Eisenberg (School of Public Health, University of Michigan)
Nina Fefferman (University of Tennessee, Knoxville)
Simeone Marino (University of Michigan Medical School)
Joseph Tien (The Ohio State University)

2017 Undergraduate Research Program

[Mostly supported by a separate NSF-REU grant]

(June 5 - August 11, 2017)

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:

- **One-week introduction (June 5-9, 2017):** A one-week introduction to the summer research experience with tutorials, lab tours, and computer labs on topics in the mathematical biosciences.
- **REU Program (June 12 - August 4, 2017):** An 8-week mentored research experience at an MBI IP on a topic in mathematical biology.
- **Capstone Conference (August 7-11, 2017):** 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.

2017 Host Institutions

1. The Ohio State University - Columbus OH

- **Focus:** Health Data Analytics, Modeling of Infectious Diseases, and Mathematical Neurosciences
- **Projects:** Identifying Genetic Maps for Predicting Survival in Leukemia Patients, Predicting Ebola Outbreaks and their Severity in Africa, A Data-Driven Weight Adjustment for Hair Cortisol Measurements as a Biomarker of Physiological Stress
- **Site Leader:** Kate Calder, Professor of Statistics (calder@stat.osu.edu)

2. Michigan State University - Lansing, MI

- **Focus:** Mathematical Molecular Biosciences and Computational Biophysics
- **Projects:** Mathematical Algorithms for Toxicity Prediction, Stability and Function of Membrane-Protein Complexes, What Mutation has Done to People Near You and How to Predict its Impact?
- **Site Leader:** Dr. Guowei Wei, Professor of Mathematics (Wei@math.msu.edu)

3. New Jersey Institute of Technology - Newark, NJ

- **Focus:** Mathematical Biology
- **Projects:** Mathematical Modeling of Ant Foraging Behavior, Modeling Slime Mold Decision-Making as Systems of Coupled Oscillators, Neuronal Oscillatory Patterns in Response to Ionic Currents, Neurobiology of Locomotion
- **Site Contact:** Dr. Simon Garnier, Assistant Professor of Biology (garnier@njit.edu)

Students, Mentors and Projects

Name	Site	Project	Mentor(s)
Bingham, Scott	NJIT	Modeling Slime Mold Decision-Making as Systems of Coupled Oscillators	Simon Garnier (garnier@njit.edu) Jason Graham (jason.graham@scranton.edu)
Sandor, Ezekiel	NJIT	Mathematical Modeling of Ant Foraging Behavior	Jason Graham (jason.graham@scranton.edu) Simon Garnier (garnier@njit.edu)
Willerth, Adam	NJIT	Neurobiology of Locomotion	Gal Haspel (haspel@njit.edu)
Vasquez-Perez, Pedro	NJIT	Oscillatory Patterns in Response to Ionic Currents	Jorge Golowasch (golowasch@njit.edu)
Korzeniecki, Nicole	NJIT	Analyzing and Modeling Dynamic Task Allocation in Leaf Cutter	Simon Garnier (garnier@njit.edu)
Poindexter, Kollin	MSU	1) Algebraic topology based machine learning approaches 2) Mathematics driven machine learning prediction of protein-ligand/drug binding affinities	Zixuan Cang (cangzixu@msu.edu)
Hourani, Fatme	MSU	1) Algebraic topology based machine learning approaches 2) What mutation has done to people near you and how to	Zixuan Cang (cangzixu@msu.edu)
Martin, Reese	OSU	Banded vegetation patterns in dryland ecosystems	Punit Gandhi (gandhi.138@mbi.osu.edu) Kate Calder (calder@stat.osu.edu)
Busch, Sydney	OSU	Predicting Ebola outbreaks and their severity in Africa	Greg Rempala (director@mbi.osu.edu) Joe Tien (jtien@math.ohio-state.edu) Marcel Yotebieng (myotebieng@cph.osu.edu) Omar Saucedo (saucedo.10@mbi.osu.edu)
Brumberg, Katherine	OSU Boston	Understanding How Prostate Cancer Risk Factors Impact Prostate Tissue Gene Expression	Jennifer Sinnott (jsinnott@stat.osu.edu)
LeBlanc, Patrick	OSU	Dependence of Homeostasis on Parameters	Janet Best (jbest@math.ohio-state.edu)
Moore, Eli	OSU	Identifying genetic maps for predicting survival in leukemia patients	Greg Rempala (director@mbi.osu.edu) Lara Sucheston-Campbell (sucheston-campbell.1@osu.edu) Maciej Pietrzak (pietrzak.20@osu.edu)

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
- 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 2016-17 (bold = leaving MBI)

1. **Casper Woroszylo** [Data Science Specialist, BHP Billiton (Australia)]
2. **Leili Shahriyari** [Applying for jobs]
3. Punit Gandhi
4. Farrah Sadre-Marandi
5. Colby Long
6. Omar Saucedo
7. Yangyang Wang
8. Reginald McGee
9. **Jeff Gaither** [The Research Institute at Nationwide Children's Hospital]
10. Min Wang

MBI Postdoctoral Fellow Hires to start in 2017

1. **Alexandria Volkening** (Applied Mathematics, Brown University)
2. **Veronica Ciocanel** (Applied Mathematics, Brown University)
3. **Colin Klaus** (Mathematics, Vanderbilt University)
4. **Amir Asiaee Taheri** (Computer Science, University of Minnesota)
5. **Inom Mirzaev** (Applied Mathematics, University of Colorado)

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. October 6, 2016, **Jeff Gaither** (MBI)
Applications of Statistical Genetics
<http://mbi.osu.edu/event/?id=1087>
2. October 13, 2016, **Leili Shahriyari** (MBI)
Computational modeling of cell dynamics in colon and intestinal crypts
<http://mbi.osu.edu/event/?id=1088>
3. October 27, **Farrah Sadre-Marandi** (MBI)
An Insight to HIV-1 Assembly through Normal Mode Analysis
<http://mbi.osu.edu/event/?id=1089>
4. November 3, 2016, **Casper Woroszylo** (MBI)
Estimation and Dynamics in Household Disease Modeling
<http://mbi.osu.edu/event/?id=1090>
5. November 10, 2016, **Min Wang** (MBI)

Thresher, A Novel Clustering Approach to Determine the Number of Clusters and Its Application to Omics Data

<http://mbi.osu.edu/event/?id=1091>

6. December 1, 2016, **Reginald McGee** (MBI)
Uncovering Functional Relationships in Leukemia
<http://mbi.osu.edu/event/?id=1092>
7. January 26, 2017, **Xiulan Lai** (Applied Mathematics, University of Western Ontario)
Exosomal miRs in lung cancer: A mathematical model
<http://mbi.osu.edu/event/?id=1115>
8. February 2, 2017, **Colby Long** (MBI)
Algebraic geometry of Phylogenetic Models
<http://mbi.osu.edu/event/?id=1116>
9. February 9, 2017, **Omar Saucedo** (MBI)
Computing Human to Human Avian Influenza R_0 via Transmission Chains and Parameter Estimation
<http://mbi.osu.edu/event/?id=1117>
10. February 29, 2017, **Ben Fogelson** (Mathematics, Utah)
Force scaling and symmetry breaking in a simple model of cell contraction and adhesion
<http://mbi.osu.edu/event/?id=1142>
11. March 2, 2017, **Punit Gandhi** (MBI)
A topographic mechanism for the arcing of vegetation bands in dryland ecosystems
<http://mbi.osu.edu/event/?id=1119>
12. March 15, 2017, **Yangyang Wang** (MBI)
Timescales and mechanisms of sigh-like bursting and spiking in models of rhythmic respiratory neurons
<http://mbi.osu.edu/event/?id=1118>
13. March 23, 2017, **Ben Fogelson** (Mathematics, Utah)
Elasticity and diffusion in the nuclear pore complex
<http://mbi.osu.edu/event/?id=1126>
14. April 6, 2017, **Maciej Pietrzak** (MBI)
Immunome profiling using entropy-based approaches
<http://mbi.osu.edu/event/?id=1120>

MBI EARLY CAREER AWARDS IN 2016-17

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

- Lin Wan - Chinese Academy of Sciences, September 2016 – December 2016
- Alan Veliz-Cuba - Mathematics, University of Dayton, January 2017 - May 2017
- Nesity Tania - Mathematics, University of Utah, January 2017 - May 2017
- Hye-Won Kang - Mathematics & Statistics, University of Maryland, February 2017 - May 2017
- Thomas Woolley - Mathematical Biology, University of Oxford, February 2017 – May

2017

- Juan Calvo - University of Granada, February 2017 - May 2017

Early Career Awards currently expected for 2017-18

- David Murrugarra – University of Kentucky, September 2017 – November 2017
- Calistus Ngonghala – University of Florida, January 2018 – May 2018
- Megan Powell – University of St. Francis, Spring 2018
- Daniel Linder – Augusta University, Spring 2018

LONG TERM VISITORS IN 2016-2017

- Tomas Alarcon – Math Biology, Centre de Recerca Matemàtica, March 2017 - April 2017
- Boseung Choi - Computer Science and Statistics, Daegu University, February 2017
- Kesh Govinder – Math Sciences, University of KwaZulu-Natal, March 2016 - March 2017
- Harsh Jain - Mathematics, Florida State University, June 2017
- Yangjin Kim - Konkuk University, December 2016 - August 2017
- Wasiur Rahman Kuda Bukhsh - Technische Universität Darmstadt, February 2017 - March 2017
- Wasiur Rahman Kuda Bukhsh - Technische Universität Darmstadt, May 2017
- Xiulan Lai - Renmin University of China, September 2016 - August 2018
- Kang-Ling Liao – The Ohio State University, May 2017 - June 2017
- Philip Maini - Mathematical Biology, University of Oxford, January 2017 - April 2017
- Maciej Pietrzak - Biostatistics, Ohio State University College of Public Health, June 2017 - December 2017
- Arnd Scheel - Mathematics, University of Minnesota, February 2017 - March 2017
- Blerta Shtylla - Mathematics, Pomona College, March 2017
- Piotr Sliwka - Mathematics & Natural Sciences, Cardinal Stefan Wyszyński University, February 2017 - March 2017
- Yane Wang - Shaanxi Normal University, March 2016 - March 2017
- Bill Kalies – Math Sciences, Florida Atlantic University, August 2017 – December 2016
- Yury Puerta Garcia – Centro de Investigación en Matemáticas (CIMAT), September 2016 – December 2016
- Kelly Spendlove – Mathematics, Rutgers University, September 2016 – December 2016
- Konstantin Mischaikow – Mathematics, Rutgers University, September 2016 – December 2016
- Tomas Gedeon, Mathematics, Montana State University, November 2016 – December 2016
- Ben Fogelson – Mathematics, University of Utah, February 2017 – April 2017
- Nourridine Siewe – University of Tennessee, April 2017 – April 2017
- Wenrui Hao – Pennsylvania State University, June 2017 – July 2017
- Boseung Choi – Applied Statistics, Korea University Sejong Campus, July 2017 – August 2017

Long Term Visitors currently expected for 2017-18

- Thomas, Peter - Mathematics, Applied Mathematics and Statistics, Case Western Reserve University, August 2017 – December 2017
- Moise Nicolae – August 2017 – September 2017
- Martin Wechselberger - Mathematics and Statistics, University of Sydney, August 2017 – September 2017
- Claire Postlethwaite - Applied Mathematics, University of Auckland, September 2017 – October 2017
- Graham Donovan – Mathematics, University of Auckland, September 2017 – October 2017
- Yiyi Zhu – Shanghai Municipal Center for Disease Control & Prevention (SCDC), August 2017 – October 2017
- Ben Fogelson – University of Utah, September 2017 – November 2017

MBI VISITOR REPORTS

Wan, Lin

Chinese Academy of Sciences

Recent years have witnessed the increasing importance of mathematical theories and methods in the study of biosciences. As an Early Career Award visitor to MBI, accordingly, I carried out my visit with the goal of developing novel mathematical theories and algorithms for the analysis of complex data in biological/biomedical systems. I view MBI as a unique hub for mathematical biosciences research that has profound resources of information and programs, allowing me to work with and learn from colleagues from different fields with overlapping research interests. Overall, I deeply appreciate this valuable opportunity of visiting, which had been very productive and fruitful and given me new insights and perspectives that will be of great importance for my future research. I would like to take this opportunity to thank all colleagues at MBI for the great support, kindness, and assistance they provided to me when I went on this meaningful trip across the Pacific Ocean.

Workshops and Seminars Attended

I have been conducting a series of modeling and statistical studies of the high dimensional spatial-temporal data in molecular biology and brain sciences. Therefore, my main goal of this visit is to attend the Fall 2016 Emphasis Semester on the Analysis of Complex Data in Biological Systems. Specifically, I attended four Workshops that include (1) Topological, Geometric, and Statistical Techniques in Biological Data Analysis; (2) Models for Oncogenesis, Clonality and Tumor Progression; (3) Dynamical Systems and Data Analysis in Neuroscience: Bridging the Gap; and (4) Population Models in the 21st Century.

These workshops greatly helped me to gain a deep understanding of the mathematical modeling and analysis of dynamical biological data since they introduced novel mathematical techniques (i.e. persistence homology) that can be useful in the analysis of dynamical data in a variety of biological systems and settings.

Moreover, I attended MBI regular seminars for visitors, postdocs, and a special topic seminar on networks. On these seminars, I was glad to present two of my accomplished and ongoing projects: (1) Modeling the Crosstalk for the High-throughput DNA Sequencing Data,

and (2) Network Modeling and Computation of Human Brain Data and Data Driven Study on Mental Disorder.

Research Collaborations

During and after the visit, I have been working with Professor Grzegorz Rempala on the goodness-of-fit tests for the generalized linear models (GLMs). We proved that the widely-used Pearson chi-square test is not chi-square but asymptotically normal distribution under the case of the sparse data within the cell (fixed covariate) for the GLMs. We then proposed new statistics for the goodness-of-fit tests of GLMs and proved their asymptotic normality. Our primary simulation results showed that the proposed new statistics have higher powers compared with Pearson chi-square test. Currently, we are working on theoretical interpretation on the performances of goodness-of-fit statistics. This work potentially can be applied to the analysis of complex biological data, such as RNA-Seq data.

During my visiting at MBI, I also initiated a collaborative research with MBI visiting Professors Konstantin Mischaikow and William Kalies on the explorative project of mapping and reconstruction of cell developmental trajectory based on the high-dimensional molecular profiles from cross-sectional single-cell data. We are developing methods and algorithms by integrating ideas from dynamical systems, geometry, statistics and machine learning to tackle this problem. The collaborative project continues after I finished my visit of MBI.

Maini, P.K. **Oxford University**

I was one of 4 co-organisers of the Semester Program “On Growth and Form” which consisted of 3 one-week workshops. I attended all three and co-organised the second in the series. I made visits to:

- University of North Texas (Denton) – to visit Dr Rajeev Azad, whom I had met at the MBI during my sabbatical in 2016
- Mexico State University (Las Cruces) – where I interacted with Professor Jianjun Paul Tian (who was at postdoc at the MBI, where I met him several years ago) and we have started working together on the manuscript “Mathematical modelling of PDGF-driven glioma reveals the infiltrating dynamics of immune cells into tumours”
- University of California (Riverside) – where I gave the Inaugural Distinguished Lecture in Mathematical Biology
- University of Cincinnati – where I met with Professors Tongli Zhang and Chris Hong. This has initiated a new collaborative project on multiscale modelling of the effects of circadian rhythm on the gut and are aiming to apply for a NIH grant in September. This collaboration will also involve my colleague Professor Helen Byrne (Oxford)
- Temple University (Philadelphia).

In total, I gave nine research talks (including two at the MBI).

A number of further collaborations have arisen from this visit:

- With Professor Ming Chuong (who was a speaker at one of the workshops) and his laboratory (University of California, San Diego), together with Dr Thomas Woolley

(visiting the MBI from Oxford, now Cardiff) we have started a new collaboration on sequential formation of feather patterns during early chick development

- With Professors Paul Kulesa (Stowers Medical Research Center, Kansas and co-organiser of Workshop 2) and Ruth Baker (Oxford – speaker at Workshop 2) we revised a research paper and re-submitted it
- With Dr Thomas Woolley I co-authored a paper on Turing pattern formation for an invited book chapter
- I initiated a collaboration with Adrian Lam, (Maths, Ohio State) on modelling somatic evolution during tumour growth.

Furthermore,

- I continued to compile papers for two special issues of the *Bulletin of Mathematical Biology* that I am co-editing with Professor Sandy Anderson (Moffitt Cancer Research Center, Tampa) on “Mathematical Models of Cancer” – this is based on the MBI Emphasis year on “Cancer and its Environment” (2014-15), co-organised by Professor Anderson
- With another co-organiser of the 2nd Workshop, Professor Mark Alber (UC Riverside), we started to discuss the possibility of a special issue based on one of the themes explored in the workshop. This proposal has now been accepted by the *Bulletin of Mathematical Biology* – “Multiscale Modelling of Tissue Growth and Shape”
- I also began reading the detailed biological background for a new collaboration I am starting with Professor Zoltan Molnar in Neuroscience in Oxford on “Mapping cortex evolution through mathematical modelling” that is funded by St John’s College, Oxford. Both Dr Woolley and I worked with the postdoc funded by this grant, who is based in Oxford, to develop new mathematical models for cell differentiation.

I arrived in January having finished off a number of projects and my goal was to try to use the workshops, visitor program, and location of the MBI, together with the mental space it offers (due to the hugely helpful staff and facilities, visitors can simply get on with science, unencumbered by administration, in comfortable surroundings) to find new collaborations and get momentum on them before going back to teaching duties at my home university. I was able to do all and I am very thankful to the MBI for allowing me these opportunities. Thank you.

Choi, Boseung **Korea University Sejong Campus**

I visited MBI February 2017 and August 2016 as a short term visitors. I think MBI is the best research space to carry out research between disciplines. First of all, well-trained and prepared staffs at BMI provide the best service to visiting researchers like myself. As soon as I arrive at the institute after a long journey, I’m able to start my research work immediately after all administrative processing has been completed.

But the most important role is that MBI is the premier research space for collaborative research among academic fields, especially in the fields of Biology, life sciences, medical science and Mathematics and Statistics.

As a statistician, I was able to meet with a number of applied mathematicians as well as statisticians to conduct joint research. As a statistician, I also was able to give advice and to meet

with biologists who were interested in solving research problems using genuine data collected from actual sites. These include Dr. Grzegorz Rempala, interim director of MBI, Dr Casper Woroszylo (Post. Doc of MBI), Professor Jiyong Lee and Rebecca Garabed (The Ohio State University), Professor Hye-Won Kang (University of Maryland Baltimore County), Dr. Mark Bunch (The Ohio State University), and Professor Jae Kyoung Kim (KAIST)
The following is a list of works I have been doing as MBI.

Seminar and meeting Attendances:

1. Colloquia by Joel Cohen (Laboratory of Populations, Rockefeller & Columbia University)
2. Visitor seminar by Kesh Govinder (Mathematics, Statistics and Computer Science, University of KwaZulu-Natal)
3. I gave a talk at MBI visitors seminar: The title is “Beyond the Michaelis-Menten equations for the unbiased estimation of enzyme kinetics”
4. I attended institute partnership annual meeting.

Research Interactions:

The major activities at MBI is to have collaborative and inter-discipline research.

1. Epidemic modeling – with Grzegorz Rempala. The classical SIR (susceptible – Infected – Recovered) model is well known method to construct the the process of disease spread. This model is to explain the process of disease spread. Various studies have been conducted to improve the prediction ability of the SIR model. Our study aimed to improve the predictive ability of the SIR model by predicting the unobserved or unreported number of infections that could be missed at the initial stage of pandemic.
2. Epidemic model using random graphs – with Grzegorz Rempala and Mark Bunch. 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. We applied the method to Ebola pandemic in West Africa and Korean MERS pandemic data.
3. Modeling household transmission in Zoonotic diarrheal disease – with Casper Woroszylo, Jiyong Lee, and Rebecca Garabed. This collaborative work focused on a method for analyzing the within-household network dynamics of an endemic zoonotic diarrheal disease in Sub-Saharan Africa based on the observational, cross-sectional data as often available from household health surveys. In this research we consider using the formalism of the dynamic SID (susceptible-infected-diseased) process which describes the disease steady-state while adjusting for the household age-structure and environment contamination
4. Enzyme kinetic modeling – with Jae Kyoung Kim and Grzegorz Rempala. Examining enzyme kinetics is critical for understanding cellular systems and for using enzymes in industry. To estimate the enzyme kinetic parameters from reaction progress curves of substrates, the Michaelis-Menten equation has been widely used for over a century. here we propose a Bayesian approach based on an equation derived with the total quasi-steady-state approximation. In contrast to the canonical approach, estimates obtained with

this proposed approach exhibit little bias for any combination of enzyme and substrate concentrations.

Tania, Nesy
Smith College

I begin this report by expressing my sincere gratitude for the support provided by the Mathematical Biosciences Institute through the Early Career Award visitor program during the Spring 2017 semester. As a junior faculty at a smaller liberal arts institution, my visit to MBI was especially valuable as it allowed me not only time but also opportunities to learn new research and develop contacts with the wider math biology community. During the duration of my visit, I was able to start several new collaborations while also working on two existing projects/manuscripts. I briefly outlined below some research highlights from my stay at MBI.

During the Modeling of Tissue Growth and Form Workshop, I was able to develop a new collaboration with Jeffrey Bush (UCSF, Dept. of Cell and Tissue Biology) who presented a poster of ongoing experimental work on cell sorting during craniofacial development. One of the primary focus of the Bush Lab is to understand how the Ephrin signaling pathway impacts cytoskeletal tension and cell---cell adhesion that then drive two populations of cells to segregate into distinct separate regions. In collaboration with Ben Fogelson (joint postdoc at University of Utah and MBI), we are currently developing cell vertex models to explore how differential adhesion and differential tension drive the cell---sorting process.

During the Women Advancing Mathematical Biology Workshop, I served as a co---leader with Helen Moore (Bristol Myers Squibb) on a research project on modeling combination therapy for multiple---myeloma. The working workshop was a productive time for our team which additionally also consists of three other junior faculty, one postdoc, and two graduate students. The research project is ongoing and we plan to submit a manuscript to the Springer volume for the workshop by November 1.

I also worked to complete the following manuscripts during my stay at MBI:

- Song S, Lee J, Trapani J, and Tania N. *Mathematical Modeling and Analyses of Interspike---Intervals of Spontaneous Activity in Afferent Neurons of the Zebrafish Lateral---Line* (Submitted).
- Cyr J, Karagiannis T. and Tania N. *Mathematical models for the regulation of cofilin on actin growth during formations of lamellipodia and lamellipodia in carcinoma* (invited book chapter for the upcoming Springer Volume on Cell Movement: Modeling and Applications).

Sliwka, Piotr
Cardinal Stefan Wyszyński University

From February 16th to March 15th 2017 I was a visitor in MBI. During this time I participated in two workshops: "The Biological Challenges in Morphogenesis" February 20 th, 2017 to February 24 th, 2017 and "Modeling of Tissue Growth and Form" March 6 to March 10 th, 2017

devoted to the processes of morphogenesis. Limited time to stay in MBI until March 15 did not allow me to participate in the third workshop "Hybrid Multi-Scale Modeling and Validation" March 27th to March 31st, which seemed to be the most interesting from the point of view of modeling.

Besides trying to apply Markov chains and Markov set chains to morphogenesis (work on these topics is still ongoing), during my stay I worked on stochastic mortality switched models. Some researchers have observed that the estimation of parameters for the same model depended on the year, for instance, the estimate of parameters during 1930-1950 gave quite different results of the parameters compared with those of 1960-1980. Therefore we would like to propose a new philosophy of constructing a model mortality that will take into account the changes of estimated parameters. We will use the methodology that has been used in control theory, economics, biology, chemistry and called "stochastic dynamic hybrid (or switched) systems", which are dynamic systems consisting of several structures described by deterministic or stochastic differential equations. The results are included in the article "A Proposition of Generalized Stochastic Milevsky-Promislov Mortality Models" (Scandinavian Actuarial Journal, manuscript under review). In this paper we first propose two extended Milevesky and Promislow models. In the first one in assume the colored excitations are modeled by Gaussian linear filters while in the second model the excitation are modeled by a continuous non-Gaussian process. To estimate model parameters using the first and second moments of mortality rates. We show in both models only a part of parameters can be estimated. Next we use these models to create hybrid models, where submodels have the same structure and possible different parameters. The exact analytical formulas for theoretical mortality rates based on Gaussian linear scalar filter models have been derived. The theoretical values obtained in both cases were compared with the theoretical mortality rates based on classical Lee-Carter model and verified on the basis of empirical Polish mortality data. The obtained results confirmed the usefulness of the switched model based on the continuous non-Gaussian process for modeling mortality rates.

In addition, based on the data: "Immunomers of patients treated with hematological malignancies" from the OSU Comprehensive Cancer Center, I began work on the determination of homogeneous groups by clustering methods. A similar analysis based on known similarity measures was performed for the data: "T-Cell receptor repertoires from prostate, draining lymph nodes and peripheral lymph nodes of mice with induced prostate cancer and age-matched controls" from Old Dominion University. Works on these topics will be continued in the fall.

I see 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.

Cheol-Min Ghim, Ph.D.
Ulsan National Institute of Science and Technology, Korea

During my visit in Mathematical Bioscience Institute (September 1, 2015 - August 31, 2016), I had been working on the following two projects in parallel:

1. Selection of heterozygosity in eukaryotic gene expression: The singlenucleotide

polymorphisms bearing the signatures of balancing selection are enriched in active cis-regulatory regions of immune cells and epithelial cells, the latter of which provide barrier function and innate immunity. Examples associated with ancient trans-specific balancing selection are also discovered. Allelic imbalance in chromatin accessibility and divergence in transcription factor motif sequences indicate that these balanced polymorphisms cause distinct regulatory variation. However, a majority of these variants show no association with the expression level of the target gene. Instead, single-cell experimental data for gene expression and chromatin accessibility demonstrate that heterozygous sequences can lower cell-to-cell variability in proportion to selection strengths. This negative correlation is more pronounced for highly expressed genes and consistently observed when using different data and methods. Based on mathematical modeling, we hypothesize that extrinsic noise from fluctuations in transcription factor activity may be amplified in homozygotes, whereas it is buffered in heterozygotes. While high expression levels are coupled with intrinsic noise reduction, regulatory heterozygosity can contribute to the suppression of extrinsic noise. We found this mechanism may confer a selective advantage by increasing cell population homogeneity and thereby enhancing the collective action of the cells, especially of those involved in the defense systems in humans.

Related publication

MK Sung, J Jang, KS Lee, CM Ghim, JK Choi, Selected heterozygosity at cis-regulatory sequences increases the expression homogeneity of a cell population in humans, *Genome Biology* (2016) 17:164.

2. Effects of symmetry breaking in synthetic gene circuits: In the realm of synthetic biology, it is of great interest to engineer genetic circuits that can change their mode of operation from monostable to bistable, or even to multistable, based on the experimental fine-tuning of readily accessible parameters. In order to successfully design robust, bistable synthetic circuits to be used as biomolecular probes, or understand modes of operation of such naturally occurring circuits, we need to identify parameters that are key in determining their characteristics. I analyzed the properties of a general, asymmetric genetic toggle switch based on a chemical-reaction kinetic description. By making appropriate approximations, I was able to reduce the system to two coupled differential equations. Their deterministic stability analysis and stochastic numerical simulations are in excellent agreement. Drawing upon this general framework, I developed a model of an experimentally realised asymmetric bistable genetic switch based on the LacI and TetR repressors. By varying the concentrations of two synthetic inducers, doxycycline and IPTG, I could predict that it will be possible to repeatedly fine-tune the mode of operation of this genetic switch from monostable to bistable, as well as the switching rates over many orders of magnitude, in an experimental setting. Furthermore, we find that the shape and size of the bistability region is closely connected with plasmid copy number.

Related publication

N Martyushenko, SH Johansen, CM Ghim, E Almaas, Hypothetical biomolecular probe based on a genetic switch with tunable symmetry and stability, *BMC Systems Biology* (2016) 10:39.

Gedeon, Tomas
Montana State University

I visited MBI during the Fall 2016 during the emphasis on Analysis of Complex Data in Biological Systems. My first visit was during the Workshop 1: Topological, Geometric, and Statistical Techniques in Biological Data Analysis in September, and then I return subsequently to spend the month of November at MBI. During this time, I participated in Workshop 4: Population Models in the 21st Century. During my time at MBI, I gave two talks in MBI seminar and in Visitor's seminar. I participated in person in one National Math Biology colloquium and several other talks. During the visit, I initiated and extended collaboration with several collaborators.

- I worked with prof. Bill Kallies from Florida Atlantic University and prof. Robert van der Vorst from Amsterdam Free University on a grant submission to Simmons Foundation.
- I worked with prof. Konstantin Mishaikow from Rutgers University on two papers, which will hopefully be submitted within a month. MBI will be acknowledged in these publications.
- I worked with Kelly Spendlove from Rutgers University on _nishing a paper that we started 3 years ago.
- I worked with visitors prof. Steve Haase (Biology) and John Harer (Mathematics) from Duke University during their two day visit. We planned NIH grant submission, worked on a Darpa contract submission, and planned next year of research collaboration on dynamics of malaria parasite.
- I have had a discussion with a postdoctoral associate Dr. Reginald McGee after my presentation.
- I had a discussion with visitor Kesh Govinder, which may lead to a future collaboration.

I very much enjoyed my stay. The staff and facilities are absolutely first rate and well designed to lead to a productive, collaborative visit.

Thank you

Wasiur R. KhudaBukhsh
Technische Universität Darmstadt

I visited the MBI twice this year. My first visit was from February 26, 2017 to March 11, 2017, and the second one was from May 5, 2017 to May 20, 2017. Both the visits were immensely rewarding and productive.

First Visit (February 26, 2017 to March 11, 2017)

I participated in the second Emphasis Workshop “Modelling of Tissue Growth and Form” (March 6-10, 2017). The workshop was particularly well organised. The schedule accommodated numerous discussion sessions that allowed people to interact and exchange scientific ideas. The speakers were all experts in their respective domains and delivered excellent talks. It was especially wonderful to hear Philip Maini from the University of Oxford. His talk on D’Arcy Thompson was inspiring. I also got the opportunity to interact with him briefly. The workshop was educational and certainly broadened my scientific perspective.

Having arrived one week before the start of the workshop allowed me to put the finishing touches to an ongoing collaboration with Greg Rempala and Casper Woroszylo. The work was started in the summer of 2016 when I visited the MBI for the first time. We derived a functional central limit theorem for the stochastic susceptible-infected (SI) epidemic model on configuration model random graphs. A natural extension of the SI model is the susceptible-infected-recovered (SIR) model. Greg and I therefore subsequently began discussing a possible extension of our result to the SIR case. However, deriving a functional central limit theorem for the SIR process seems tricky. Both Greg and I hope to complete this project in future.

It was wonderful to meet Hye-Won Kang during my stay there. Greg, Hye-Won and I started brainstorming about some problems related to what are known as the quasi-steady state approximations (QSSAs). Hye-Won was wonderful to collaborate with. Greg, Hye-Won and I spent quite some time in front of the white board and managed to get some success with our ideas. We continued working on this during my second visit as well.

I also attended several other talks during my stay there. The talks by Punit Gandhi, Ben Fogelson and Kesh Govinder were interesting. Kesh Govinder's group theoretic approach was compelling.

Second Visit (May 5, 2017 – March 20, 2017)

My second visit this year was in May. This time also I stayed there for two weeks. Greg introduced me to Juan Calvo. Juan was interested in a certain type of chemical reaction in a random environment. We discussed at length and adopted a marginalized approach to model the chemical reaction of his interest. It still has to be seen how the proposed method fares. Nevertheless, this is a new potential collaboration.

Greg, Hye-Won and I continued working on the project that we started during my previous visit. It was on the QSSAs. We managed to produce the first draft of our paper. We are now planning to submit it. It was very productive. Apart from the QSSAs, in the meanwhile Greg and I started working on some asymptotic aspects of chemical reactions. Greg and I spent hours to have a better understanding of the problem and its possible solution. We did not get enough time to achieve a breakthrough, but both of us are hopeful! We shall continue working together.

During this visit of mine, I had the chance to attend talks by Tim Elston and Qing Nie. Both Tim Elston and Qing Nie delivered very interesting talks. Both were excellent communicators of their respective research findings. I also attended a seminar talk by Chuan Xue. She talked about derivation of continuum models from individual-based models for chemotaxis of bacterial populations.

My time at the MBI has been very productive and fulfilling. I came to know a host of motivated researchers. I began collaborations that I expect to go on for the years to come. Greg, in particular, has not only been a great collaborator, but also a mentor. Many thanks to him. It was very kind of MBI to allow me to attend the postdoc seminars even though I was not a postdoc at MBI. Last but not the least, I must thank the entire MBI team for all the fun get-togethers, and for their wonderful hospitality.

Talks attended:

1. Tim Elston
2. Ben Fogelson (MBI postdoc)
3. Punit Gandhi (MBI postdoc)
4. Kesh Govinder (MBI visitor)
5. Qing Nie
6. Chuan Xue (Math., OSU)

Workshop attended:

1. Emphasis Workshop “Modelling of Tissue Growth and Form”

Collaborations:

1. Greg Rempala (MBI)
2. Hye-Won Kang (MBI visitor)
3. Casper Woroszylo (MBI postdoc)
4. Juan Calvo (MBI visitor)

Woolley, Thomas
Oxford University

I joined the MBI during the 2017 spring emphasis program on Growth and Morphogenesis. I had been particularly interested in attending this set of workshops, as my doctoral work had involved researching stochastic pattern formation on growing domains. Thus, the program aligned perfectly with my research interests.

Moreover, Columbus was a great location to use as a base in order to visit numerous other American universities. Thus, not only was I treated to world experts presenting their cutting edge mathematical biology research at the workshops and weekly seminars but I could also expand my collaboration network by speaking at numerous other universities.

The work I focused on, whilst at the MBI, involved the creation of complexity from simplicity, i.e. morphogenesis. The field of morphogenesis has, for a long time, depended on Turing’s theory of diffusion driven instability in order to be able to produce spontaneous pattern formation. Although a beautiful subject, both in terms of the theory and simulations, it has yet to be proven to exist biologically.

More recently, work in Japan has shown that the cells that form the stripes in zebrafish interact through a chiral chasing mechanism. Specifically, one cellular family (which produces the white stripes) chases after a different cellular family (which produces the black stripes).

Critically, a mathematical framework of this chasing mechanism had already been produced. However, it lacked a core ingredient of the intrinsic chiral motion of the cells. Namely, although the cells chase after one another, they don’t follow each other directly. Rather, the chasing cells move at an angle directed away from the cells being chased, resulting in a spiralling motion.

My intention was to derive a mean-field system of partial differential equations that included this chiral chasing. Not only was the aim to make the model more realistic, but my goal was to test a

current biological hypothesis that the microscale interactions could influence the macroscale patterning. This hypothesis was created by noticing that mutant zebrafish with different patterns (e.g. spots, or broken lines) also had cells with altered chirality.

My first month was spent enacting a literature review, in order to (a) check that no one had produced a similar model; and (b) read the current work that had incorporated the chasing mechanism. I then began to develop and extend this previous framework in order to allow for the chiral movement.

During this month I met with many of the post-docs and other MBI visitors. It was pleasing to find such a sociable and interesting group of people. The diverse array of research in the Institute is extremely impressive and I was able to learn a lot from the local expertise. This knowledge was a benefit from both an academic point of view, as well as from a social point of view. Specifically, in terms of navigating my way around the city, finding good restaurants, watching new spots and building a social life in a new city, far from home. I felt very accepted by the department and this made me very happy.

On the research front, I was particularly interested in Punit Ghandi's work, as it was closely related to my own. He presented a new type of patterning mathematics that I had not seen before, which I've since been able to use in my own work.

Equally, I was very interested in the network theory of Alan Veliz-Cuba. I am very new to the area of network theory and I found Alan's talks to be enlightening. I hope to use some of his techniques in the future.

Alongside learning from people in the department, I hope that I will aided others. Specifically, I showed Omer Saucedo how to speed up his simulations through parallelisation and I demonstrated how to use COMSOL to Punit Ghandi and Juan Calvo.

During February I also visited the Stowers Institute for Medical Research in Kansas City. Although I was only there for a few days I met a number of biological experimentalists who were very open to using mathematical modelling. From these meetings I developed a collaboration with Paul Kulesa and hope to develop new collaborations in the future.

Finally, during February I attended the first in a series of workshops. During the workshop I worked with Colby long and Punit Ghandi to produce concise summaries of each talk. This summarising process was a useful practice as it meant that I had to maintain focus even on the talks that weren't necessarily in my research area. This meant I got a lot more out of the workshop than I would have otherwise.

The second month of work was focused on developing the new mathematical framework in which the modelling would fit. Although theoretically straight forward my time was stretched quite thin, as March contained two week-long workshops. Thus, I had to develop better time management skills in order to balance my work with the presentations.

During this month I also received the chance to work with COSI and do an outreach presentation at one of their adult only evenings. The theme of the night was puzzles and I illustrated how mathematics could help the audience solve many of the problems that they might face when they go on holiday. The whole evening went very well and I was excited to see as many of the other displays as I was to present my own.

My second external visit was to see the lab of Cheng-Ming Chuong at the University of South California. He is a pioneer in experimental pattern formation and his work on feather bud formation was of particular interest to me. Whilst I was there I spoke to a number of his research associates and I am currently collaborating with one of them, with the potential of forming collaboration soon.

My proudest moment was at the very end of the March, when I finally simulated my theory. Not only were patterns formed, but the patterns were unlike any others that I had ever seen in the wider literature. This made me very excited and I continued my numerical investigations over the coming weeks in order to explore the new patterning possibilities of the chiral chasing mechanism.

My final two visits occurred in April and these were to the universities of Michigan and Wisconsin. These visits were rather different from the previous two as I was visiting mathematics departments or numerically led labs, rather than purely biological departments. This meant that I was focused more on illustrating the techniques that I had pioneered in my research, rather than try to develop new collaborations. My work was well received and I look forward to discussing new ideas in the future with many of the colleagues that I met at these institutions.

As the month drew to a close I had finished the first draft of the chiral chasing write up. Although it would still be another month until it was ready to be submitted I had, at least, presented all of my ideas on paper.

In summary, I really enjoyed my time at the MBI. Not only was I able to produce some new work, but I was able to dramatically grow my collaborator network. As I was moving on to a permanent position shortly afterwards this was the perfect time to go out and travel around America in order to gain and deliver new ideas. I truly hope that I will return to the MBI one day with the aim of meeting a brand new set of people and develop new ideas.

Yane Wang
Shaanxi Normal University in China

I am very thankful to Prof. Lou Yuan who invited me as a visitor scholar at MBI from March 4 2016 to March 4 2017. I really appreciated the help from colleagues of MBI in my study and life in Columbus.

My research focus is on the theory and applications of reaction-diffusion equations. During this year, first, on one hand I mainly attended the seminars or workshops at MBI to know other scholars' research fields, on the other hand, I read some classic works of Prof. Lou and his coworkers and now have deeper thoughts on my work. After that, I began to write my papers. I finished an article about a general activator-substrate biological depletion model which described

by a reaction-diffusion model. The existence of non-constant solutions of this model was studied. Another research on the Lotka–Volterra advection diffusion model and a phytoplankton model was in progress before I came back to China.

I was deeply attracted by the beautiful campus and the strong academic atmosphere in MBI. Colleagues of MBI are diligent and enthusiastic. During the visit of MBI, I made some good friends and broadened my horizons.

Thanks to all of you.

Schell, Arnd
University of Minnesota

Report on visit to the MBI

I visited the MBI in the period Feb 15-March 10, for 23 days. Within this period, I participated in two one-week long workshops at the MBI, and gave a presentation at the Department of Mathematics.

Prior to this visit, I had developed an interest into morphogenesis, from a pattern formation point of view, striving to describe the interplay of pattern formation and apical growth, which was the subject of my presentation in the department of mathematics. My primary goal for the visit was to get an overview of the current state of research in morphogenesis, in particular in regards to pattern formation. From that perspective, the two workshop provided an ideal venue for a novice in this area, I could not have been happier with the time invested.

Key interactions that i am currently pursuing further is the influence of prepatterning (group of Dagmar Iber, Zuerich) on selection of patterns, and the effect of signal gradients on patterns (group of James Sharpe, Barcelona; Sean Megason, Harvard). A graduate student is currently exploring connections to our work.

In addition, I had many fruitful discussions with Punit Ghandi, currently an MBI postdoc, who has been working with the group of Mary Silber on ecological modeling, namely the appearance and orientation of striped patterns in semi-arid vegetation zones. Punit will be mentoring an REU student this summer on these problems, while I will be hosting an REU project in Minnesota on related topics. We plan to interact during the REU and possibly beyond.

Although not started at the MBI, my current work includes the study of patterns in bacterial colonies, governed by run-and-tumble mechanisms. A first paper had appeared in JMB. I am currently extending this work, isolating "thermodynamics phase boundaries" in a simple run-and-tumble model. We show the existence of three "phases": spatially uniform concentration, ripple patterns, and formation of aggregates, described mathematically as blowup. All three phases are separated by comparatively small changes to the tumble mechanism in the form of a parameter change. I had many stimulating conversations during workshops, that greatly informed the current direction of this research, for instance with Mark Alber (Riverside).

Veliz-Cuba, Alan
University of Dayton

The main topics that I worked on during my time at MBI are the following.

- **An algebraic approach for network reconstruction of discrete dynamical systems** (manuscript, in preparation). In this project, I am generalizing previous results of using algebraic tools to recover the structure of gene regulatory networks from time-series data. Previous results focus on finite dynamical systems, but real data is continuous and noisy. Thus, I am generalizing the algebraic approach I developed in the past to also work on continuous and noisy data. In summary, given time-series from a gene regulatory network, one can encode the data as an algebraic structure. This algebraic structure can be analyzed using tools from algebraic geometry. In particular, we can use these tools to infer the structure of the network that best fits the data. Furthermore, with probability 1, the true network will eventually be recovered. This is true even in the presence of noise.

- **Stable steady states of conjunctive ODE systems** (manuscript, in preparation). This project is about counting and finding the stable steady states of gene networks constructed with AND gates. A gene network constructed with such gates can be modeled using conjunctive ODE systems. This family of ODEs is important because it can be constructed in the lab using tools of synthetic biology. These systems are not linear and there are few tools to analyze them. Using tools from combinatorics I found a relationship between the structure of the network and the stable steady states. Such relationship can be used to predict the number of stable steady states of arbitrary networks or to design networks with a desired number of stable steady states.

- **Model analysis of discrete dynamical systems** (book chapter, in preparation). Here I wrote a book chapter containing several tools for model analysis of Boolean networks. This modeling framework is becoming more popular, so there is a need of a source where researchers and students can look up theory, algorithms, and software.

- **Analysis of combinatorial neural codes: an algebraic approach** (book chapter, in preparation). Here I wrote a book chapter aimed at teaching undergraduates algebraic tools used in neural networks.

- **Stochastic models of neural and gene networks** (grant proposal submitted to the Simons Foundation, awarded in June 2017). I submitted a grant proposal to the Simons Foundation to investigate stochastic models of gene and neural networks. The proposal got funded and will allow me to travel to work with several collaborators.

- My stay at MBI allowed me to meet a diverse group of researchers working in exciting areas. The workshops were very useful to learn about research done at other institutions and to find potential collaborators. I also visited collaborators at the University of Houston, Rice University, University of Cincinnati, and Clemson University.

In summary, my time at MBI has been extremely useful to advance all aspects of my career. The Early Career Award program is very useful and can have a profound benefit in the professional

life of young faculty.

Garcia, Yury

Centro de Investigación en Matemáticas (CIMAT)

I visited MBI from September to November. During this time, I attended the Fall Emphasis Workshop on Complex Data Analysis in Biological Systems and second Workshop on Omics Data Analysis. I also worked with Dr. Tien (OSU Math) on a problem of modeling the dynamics of Zika and Dengue. In this case, we proposed the problem and a working plan to continue once I return to Mexico. On the other hand, I also worked with Dr. Oksana Chkrebtii (OSU Statistics) on one of my PhD thesis problems related to persistence of multiple strains of viral infection in a population. We were able to make a significant progress on the model and are currently preparing the manuscript for possible publication.

Kalies, William

Florida Atlantic University

During my visit at the MBI, I collaborated with Konstantin Mischaikow on a paper that is not yet completed for submission, Lattice Structures of Attractors 3: Morse Decompositions. I also had several discussions with Lin Wan concerning a possible collaboration on discovering partial orders (in time) of data from distance matrices. Unfortunately, we have not been able to follow up on this line of research in Spring 2017, but I plan to re-connect with him this summer. I also had discussions with Tomas Gedeon and Kelly Spendlove.

The first workshop on Topological, Geometric, and Statistical Techniques in Biological Data Analysis inspired me to jump-start new research in the area of Topological Data Analysis. Upon returning to FAU in Spring 2017, I began collaborating with an FAU colleague Koray Karabina on using persistent homology to process and analyze biometric data in a secure way. We have some preliminary results, but a first paper has not been completed yet.

As a result of the collaboration with Koray Karabina, I led a group of faculty to run a special topics course in Topological Data Analysis during Summer 2017 where four faculty members and seven graduate students are discussing current techniques in TDA and how they might be applied to several applications in not only secure biometrics but also time series analysis and the topology of random manifolds. One Ph.D. student from the FAU Center for Complex Systems and Brain Science has already found new results in her own time series data from coordinated rhythmic movements and intrapersonal coordination of oscillatory neural activities. A change in coordination was discovered from a strong change in persistent homology, and she is investigating whether TDA can replace coordination detection by eye, which will be necessary to analyze larger data sets.

Calvo, Juan

University of Granada

In this report I describe my activities at the Mathematical Biosciences Institute (MBI) during the MBI emphasis program on Growth and Morphogenesis", which took place during the second

semester of the academic term 2016-2017. I am currently based at University of Granada (Spain), Applied Maths Division. My expertise is in mathematical models involving partial differential equations; some of my published works are connected with mathematical modeling for morphogen propagation. Current work in progress includes topics related with morphogenesis and proliferation of cancerous tumors, which suit the scope of the aforementioned program.

My initial idea during my visit was to develop several aspects related to hybrid multiscale computational methods and applications to the modeling of tissue proliferation. These methods try to describe at a reasonable computational cost complex systems for which stochastic effects need to be taken into account. The heart of their philosophy is to combine in a reasonable way continuous models (in those parts of the system in which a mean field description works fine) with discrete, stochastic ones (for those parts of the system in which random effects play an important role). During this period I was able to conclude a work concerning generalizations of hybrid methods to the context of (age) structured populations, in collaboration with Tomás Alarcón (MBI visitor during March 2017) and coworkers. Following this line, I initiated during my visit a collaboration with Hye-Won Kang (Early Career awardee during this emphasis semester) and Tomás Alarcón. We have made progress concerning the development of criteria for fast mixing in the context of hybrid deterministic-stochastic representations for structured populations. This provides useful guidelines for cell size selection in the implementation of hybrid simulation algorithms and paves the way to formulate and test convergence notions for this set of methods. I also obtained some preliminary results about stochastic models for protein polymerization (“Lag times and catalysis for stochastic polymerization models”, to appear in the proceeding of the CEDYA/CMA 2017 meeting of the Spanish Society for Applied Mathematics) that can be the basis to extend hybrid simulation methods to this context, where stochastic effects play an important role at small aggregate sizes. Moreover, I started another collaboration with Hye-Won Kang, Wasiur R. Khuda (MBI visitor during spring 2017) and Greg Rempala (MBI interim director); this collaboration concerns stochastic modeling of genetic regulation networks, time scale separation and averaging methods for those, in the context of multiscale models for morphogenesis.

Several events took place during my stay at MBI. I attended the following workshops:

- The Biological Challenges in Morphogenesis (Feb. 20th-24th)
- Modelling of Tissue Growth and Form (March 6th-10th)
- Hybrid Multi-Scale Modelling and Validation (March 27th-31st)

I also attended regularly the Visitor Seminar Series, where the visitors enrolled for this emphasis program lectured about their research. I contributed to this series by delivering the talk entitled “Describing Shh spreading in the neural tube using finite-propagation-speed models” (April 11th). I got involved in the Cell Motility discussion group, which was created ad hoc during this emphasis semester for visitors and postdocs at MBI to discuss topics of common interest and as a vehicle to initiate new collaborations. This team met at Friday afternoon on a regular basis during the aforementioned period. I lectured in this forum about computational hybrid multiscale methods. I also took the opportunity to attend several seminars at the OSU Maths department.

The workshops have been extremely interesting for me to get a wider view of possible research directions in those fields. During my visit I got the chance to meet a large number of researchers (postdocs, ECAs, short-term visitors) and get exposed to many different viewpoints on a number of interesting problems. I also think that my particular combination of competencies and my view on the subjects of this program has contributed to enrich the interactions and discussions that took place during this period at MBI. Getting to know the way in which MBI works is also interesting for me as there may be future chances for additional research visits, event organization and additional types of interaction. Overall, I am extremely satisfied about the development of my visit to MBI and I think that the contacts that I made during this period can crystalize in long-lasting collaborations around a number of topics related with (but not only restricted to) the scope of this emphasis semester.

Shtylla, Blerta
Pomona College

I visited MBI during a pre-tenure sabbatical from my institution, Pomona College in March of 2017. Below I outline the main activities that I participated in during my stay.

Workshops attended: Part of the purpose of my visit was to attend workshops that were held as part of the Growth and Morphogenesis Emphasis semester. During my visit I attended two great workshops: Workshop 2: Modelling of Tissue Growth and Form, and Workshop 3: Hybrid Multi-Scale Modelling and Validation. These workshop are relevant to my area of research, so it was great to participate and meet some of the speakers. Further, the problems posed and discussions were interesting in the context of exploring open problems in the field. I also found the talks interesting in the context of teaching, as every spring I teach a course in mathematical modeling. This is an advanced undergraduate course where we spend some time on pattern formation mechanisms and I came out of the workshops with great ideas on new topics to cover.

New Collaborations: During my visit I had an opportunity to discuss new projects with one MBI postdoc, Ben Fogelson on reduced models of bias generation for hydrolysis driven molecular motors. We developed a streamlined modeling framework and plan to follow up with analysis. In addition, I started a new collaboration with long term visitor Nessay Tania, on a project of Ca^{2+} wave propagation during early fertilization events in *C. elegans* oocytes. For this project, I have an experimental collaborator at my institution and Nessay is already participating via Skype in our joint group meetings. We had Nessay visit us in person once in May 2017 to meet up with my collaborator. We intend to continue our collaboration and have plans to pursue various models related to Ca^{2+} wave propagation in *C. elegans* oocytes. This visit also allowed me to reconnect with Adriana Dawes and we designed a follow up project on *C. elegans* spindle orientation that I am pursuing this summer with the help of a summer undergraduate student, who was coincidentally an MBI REU participant the previous year. During my visit, I also presented in the MBI visitor series, after which I had very productive exchanges with other MBI visitors in connection to the results presented in my talk.

Networking: During my stay I had a chance to meet several of the MBI postdocs and talk about their research and career plans. In conjunction with Nessay Tania, we organized an informal lunch

discussion with postdocs about careers in small liberal arts colleges. The conversation was lively and both Nussy and I got a chance to connect with MBI postdocs and offer any advice we had on career choice and particularly on negotiating a startup package in our type of institution.

Overall, I feel like I had a very productive stay, forged new research connections and left the institute charged and excited about new research opportunities as well as exciting ideas about teaching. I had a chance to return for two additional research workshops that same Spring and look forward to visiting and also bringing students along in the near future.

OHIO STATE UNIVERSITY COURSE RELEASE VISITORS IN 2016-2017

Fall Semester

- Oksana Chkrebtii (Statistics)
- Adrian Dawes (Mathematics)
- Avner Friedman (Mathematics)
- Adrian Lam (Mathematics)
- Shili Lin (Statistics)
- Aleix Martinez (Electrical and Computer Engineering)
- Facundo Memoli (Mathematics and Computer Science)
- Joe Tien (Mathematics)

Spring Semester

- Keith Gooch (Biomedical Engineering)
- Chuan Xue (Mathematics)

COURSE RELEASE REPORTS

Fall 2016

Oksana Chkrebtii

Assistant Professor, Statistics

The following activities were conducted during my course release in Autumn 2016. I mentored and began a collaboration with the MBI visitor Yury Elena Garcia-Puerta. We are currently in the final stages of writing a paper about this work and plan to continue our collaboration in the future. I gave a visitor seminar at MBI about my research titled “Inference for dynamical systems: a Bayesian perspective”. I also led a discussion on professional development for MBI postdocs. I attended many interesting seminar talks from the semester’s workshops, and actively participated in the workshop “Population Models in the 21st Century” from November 14 to November 18, 2016.

Adriana Dawes

Assistant Professor, Mathematics

- I attended portions of all four Workshops

- I attended the Monday network seminar, long term visitor seminar and postdoc seminar
- I was scheduled to present during the Fall term but my talk was postponed to the Spring because of construction at the MBI
- I arranged longer one-on-one meetings with several long and short term MBI visitors including Philip Maini, Helen Byrne, Blerta Shtylla, Wanda Strychalski and Mark Lewis
- I also started as Associate Director of the MBI, which involved attending meetings and participating in MBI activities which in the Fall included reviewing files and interviewing candidates for MBI postdoctoral positions.

Avner Friedman

Distinguished University Professor, Mathematics

During the past year I worked with MBI postdocs Wenrui Hao and Xiulan Lai, and MBI visitors Nourridine Siewe.

Publications with Wenrui Hao:

- (with W. Hao) *Mathematical model of Alzheimer's disease*, submitted to BMC Systems Biology, (2016) 10:108 DOI:10.1186, 18 pages.
- (with W. Hao, S. Gong, S. Wu, J. Xu, and M. Go) *A mathematical model of aortic aneurysm formation*. PLoS ONE, accepted.
- (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.
- (with W. Hao) *The role of exosomes in tumor microenvironment*, Bull. Math. Biology, accepted.

Publications with Xiulan Lai:

- (with X. Lai) *Exosomal miRs in lung cancer: A mathematical model*, PLoS ONE, (2016) DOI:10.1371 27 pages.
- (with X. Lai) *Exosomal microRNA concentrations in colorectal cancer*, J. Theor. Biol., Vol 416 (2017), 70-83.
- (with X. Lai) *Combination therapy of cancer with cancer vaccine and immune check point inhibitors: A mathematical model*

Publication with former MBI postdoc W. C. Lo:

- (with W-C. Lo, V. Arseulescu, R. Arseulescu) *Inflammatory Bowel Disease: How effective is TNF- α suppression?* PLoS ONE, (2016) DOI:10.1371, 19 pages.

I attended many lectures in the MBI workshops, and served on the LSAC.

There is also ongoing work with MBI long term visitor Yangjin Kim (in collaboration with Balveen Kaur in the medical school), with N. Siewe on HBC, and with Lai (with R. Wesoloski and W. Carson in the medical school).

Adrian Lam

Assistant Professor, Mathematics

-Submitted a NSF grant proposal.

Published five papers:

- H.-B. Hsu, K.-Y. Lam and F.-B. Wang (2017)
Single species growth consuming inorganic carbon with internal storage in the unstirred chemostat
J. Math. Biol., in press, 51pp.
- K.-Y. Lam (2017)
Stability of Dirac Concentrations in an Integro-PDE Model for Evolution of Dispersal
Cal. Var. PDE, (2017) 56: 79.
- M. Golubitsky, W. Hao, K.-Y. Lam and Y. Lou (2017)
Dimorphism by singularity theory in a model for river ecology
Bull. Math. Biol., 79 (2017), 1051-1069.
- R.S. Cantrell, X. Cao, K.-Y. Lam and T. Xiang (2017)
A PDE model of intraguild predation with cross-diffusion
Discrete Contin. Dyn. Syst. Ser. B, in press.
- K.-Y. Lam and Y. Lou (2017)
An integro-PDE model for evolution of random dispersal
J. Funct. Anal., 272 (2017), 1755-1790.

-Participation in MBI Colloquium and Visitor's seminar. Gave a talk in the latter.
-Participation in Workshop 4: Population models in the 21st Century
-Interaction with visitors, including Konstantine Mischaikow, Arnd Scheel.

Shili Lin
Professor, Statistics

List of my MBI activities in the academic year 2016-2017.

-Participated in the discussions on organizing the Fall 2018 workshops
-Participated as an audience in two Fall 2016 Workshops:

- Workshop 1: Topological, Geometric, and Statistical Techniques in Biological Data Analysis.
- Workshop 2: Models for Oncogenesis, Clonality and Tumor Progression

-Participated as an audience in the following seminars:

- Finding genes via Relatedness and the Co-ancestry of Genome
- Elizabeth Thompson - Department of Statistics, University of Washington
- Online Colloquium - Wednesday, November 9th, 2016
- Several long-term visitors seminars
- Other special seminars

-Gave a visitor seminar in April 2017; title of talk "Modeling and Inference for Spatial Chromatin Interactions", which ties closely with the topics of Workshop 1.
-Participated as an instructor in the "2nd Workshop on Omics Data Analysis".

-Invited Elizabeth Thompson to give a talk in the National Colloquium series. Title of her talk: “Finding genes via Relatedness and the Co-ancestry of Genome”

Aleix Martinez

Professor, Electrical and Computer Engineering

My primary goal was to develop a computational model of the perception of facial expressions of emotion. Specifically, I propose a new mathematical model that explains the otherwise contradictory results described in the literature. The proposed model propound that the human visual system is tasked to recognition facial actions (typically called action units, AUs). The recognition of these AUs defines an affine space that is used by the cognitive system to categorize emotions and define continuous variables such as valence and arousal. I’ve published these results in two papers:

- Martinez, A.M. Visual Perception of Facial Expressions of Emotion. Current Opinion in Psychology, in pressMartinez, A.M. Visual Perception of Facial Expressions of Emotion. Current Opinion in Psychology, in press.
- Martinez, A.M. A Computational Models of Face Perception. Current Directions in Psychological Science, in press.

I also presented these results in a seminar at MBI in November 2016.

Facundo Memoli

Associate Professor, Mathematics

-Work done while on MBI course release:

-Mentoring: I was mentoring 5 grad students and 2 undergrads.

-Grant writing: I was involved in the submission of 2 NSF grants.

-Seminars: gave talks in the MBI seminar series, and in a workshop organized by MBI.

Participated in the TGDA seminar in the Math dept. Organized special session at the AMS sectional meeting in NCSU (Nov. 12-13,2016).

Some papers I worked on:

<https://arxiv.org/pdf/1608.05432.pdf>

<https://arxiv.org/pdf/1701.00565.pdf>

<https://arxiv.org/abs/1702.07893>

-Others: I designed a mini-course on Network Data Analysis: Metrics and Persistent Homology: <https://research.math.osu.edu/networks/nda17/nda17.html>

The course took place in January 2017 in Mexico.

Joe Tien

Associate Professor, Mathematics

Participated and gave a talk at the workshop: Population models in the 21st century.

Gave a talk in the MBI Visitor Seminar.

Collaborations: with Marisa Eisenberg, on changes in infectivity and contact over the course of infection, with specific application to influenza. This is in collaboration with the Household Influenza Vaccine Effectiveness (HIVE) study at U. Michigan. Course release facilitated an in-person meeting between students and collaborators for this project. This project has resulted in an MS thesis in mathematical biology at OSU (Willa Skeeahan), and an MPH capstone project at U. Michigan (Kyle Bagshaw). We are currently developing a manuscript for submission to a peer-reviewed journal, based on Willa Skeeahan's thesis work.

Course release also provided time for developing a collaboration with Bill Miller and Abby Norris Turner on study of syphilis in Columbus in the men who have sex with men community. We wrote a CDC grant, "Syphilis epidemiology in Columbus, Ohio: A cohort and network study" (PIs: Miller and Turner), submitted in fall 2016 that was awarded in May 2017 (1.6M, 3 years). This grant involves several different units at OSU (e.g. Epidemiology, Biostatistics, Medical School, Mathematics) and includes partnership with Columbus Public Health.

Completion of manuscript "A generalized inverse for graphs with absorption", with former MBI postdoc Karly Jacobsen. Course release helped with finalizing this manuscript (currently it is under review at Linear Algebra and its Applications).

Mentoring: I worked with Omar Saucedo (MBI postdoc) on a project on vector-host disease dynamics on mobility networks. We have continued this work and are developing a manuscript (anticipated submission: summer 2017).

Spring 2017

Keith Gooch

Professor, Biomedical Engineering

As part of my MBI course release, I attend two workshops (Biological challenges of Morphogenesis Modeling Tissue Growth and Form) and presented a seminar (Agent-Based Modeling of Cell-Matrix Interactions). I also spent on average 1 day per week working in the MBI office provided to facilitate informal interactions.

Chuan Xue

Assistant Professor, Mathematics

- I attended more than half of the visitor seminars and all the MBI director job talks.
- I gave a visitor seminar.
- I participated the cell motility journal club and gave several presentations.
- I am directing MBI visiting postdoc Xiulan Lai on a joint project.

MBI 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 2016-2017 MBI Long Term Visitor Seminar speakers were:

1. September 20, 2016, **Facundo Memoli** (Mathematics, Ohio State)
A brief introduction to persistent homology via an application to neuroscience
<http://mbi.osu.edu/event/?id=1081>
2. October 4, 2016, **Lin Wan** (Chinese Academy of Sciences)
Modeling the crosstalk for the High-throughput DNA Sequencing Data
<http://mbi.osu.edu/event/?id=1094>
3. October 11, 2016, **Oksana Chkrebtii** (Statistics, Ohio State)
Inference for dynamical systems: a Bayesian perspective
<http://mbi.osu.edu/event/?id=1095>
4. October 25, 2016, **Yury Puerta** (Center for Investigations in Mathematics (CIMAT))
Stochastics Amplification in a two Pathogen epidemic Model
<http://mbi.osu.edu/event/?id=1096>
5. November 1, 2016, **William Kalies** (Mathematics, Florida Atlantic University)
Set-Based Computations for Global Dynamics
<http://mbi.osu.edu/event/?id=1098>
6. November 8, 2016, **Tomas Gedeon** (Mathematical Sciences, Montana State University)
Examining the dynamics across network space using Database for Dynamics
<http://mbi.osu.edu/event/?id=1083>
7. November 22, 2016, **Aleix Martinez** (Electrical and Computer Engineering, Ohio State)
The Face of Emotion: A computational model of the production and visual perception of facial expression of emotion
<http://mbi.osu.edu/event/?id=1084>
8. November 28, 2016, **Joe Tien** (Mathematics, Ohio State)
Contact affects disease affects contact: the interplay of infection and contact structure
<http://mbi.osu.edu/event/?id=1085>
9. December 6, 2016, **King-Yeung Lam** (Mathematics, Ohio State)
Evolution of Diffusion Rate in a Mutation-selection Model
<http://mbi.osu.edu/event/?id=1086>
10. December 13, 2016, **Kelly Spendlove** (mathematics, Rutgers University at New Brunswick)
Toward a Computational Homological Theory of Dynamics
<http://mbi.osu.edu/event/?id=1108>
11. January 17, 2017, **Yane Wang** (Shaanxi Normal university)
Steady-State Bifurcation for a Biological Depletion Model
<http://mbi.osu.edu/event/?id=1125>
12. January 24, 2017, **Alan Veliz-Cuba** (Mathematics, University of Dayton)
On the Perfect Reconstruction of the Structure of Dynamic Networks

- <http://mbi.osu.edu/event/?id=1121>
13. January 31, 2017, **Philip Maini** (Wolfson Center for Mathematical Biology, University of Oxford)
Modelling Invasive Processes in Biology
<http://mbi.osu.edu/event/?id=1122>
 14. February 7, 2017, **Nessy Tania** (Mathematics, University of Utah)
Modeling Actin Regulations in Motility Structures of Cancer
<http://mbi.osu.edu/event/?id=1123>
 15. February 14, 2017, **Boseung Choi** (Applied Statistics, Korea University-Sejong Campus)
Beyond the Michaelis-Menten equations for the unbiased estimation of enzyme kinetics
<http://mbi.osu.edu/event/?id=1124>
 16. February 27, **Kesh Govinder** (Mathematics, Statistics, and Computer Science, University of KwaZulu-Natal)
Application of symmetry methods to Mathematical Biology
<http://mbi.osu.edu/event/?id=1141>
 17. March 13, 2017, **Alan Veliz-Cuba** (Mathematics, University of Dayton)
Boolean modeling of gene networks
<http://mbi.osu.edu/event/?id=1128>
 18. March 14, 2017, **Blerta Shtylla** (Mathematics, Pomona College)
Spatiotemporal protein patterns: The mathematics of bacterial cell division
<http://mbi.osu.edu/event/?id=1127>
 19. March 20, 2017, **Facundo Memoli** (Mathematics, Ohio State)
Metric Structures on Networks
<http://mbi.osu.edu/event/?id=1144>
 20. March 21, 2017, **Alan Veliz-Cuba** (Mathematics, University of Dayton)
Controlling differentiation patterns with AND gates, preliminary report
<http://mbi.osu.edu/event/?id=1143>
 21. April 3, 2017, **Thomas Woolley** (Center for Mathematical Biology, University of Oxford)
Power spectra and weak noise methods
<http://mbi.osu.edu/event/?id=1145>
 22. April 4, 2017, **Thomas Woolley**, (Center for Mathematical Biology, University of Oxford)
Power spectra of stochastic reaction diffusion equations on stochastically growing domains
<http://mbi.osu.edu/event/?id=1129>
 23. April 10, 2017, **Keith Gooch** (Biomedical Engineering, Ohio State)
Agent-Based Model of Cell-Matrix Interactions
<http://mbi.osu.edu/event/?id=1146>
 24. April 11, 2017, **Juan Calvo** (University of Granada)
Describing Shh spreading in the neural tube using finite-propagation-speed models
<http://mbi.osu.edu/event/?id=1130>

25. April 17, 2017, **Hye-Won Kang** (Mathematics, University of Maryland Baltimore County)
Multiscale stochastic reaction-diffusion algorithms for biochemical networks
<http://mbi.osu.edu/event/?id=1132>
26. April 18, 2017, **Shili Lin** (Statistics, Ohio State)
Modeling and Inference for Spatial Chromatin Interactions
<http://mbi.osu.edu/event/?id=1131>
27. May 1, 2017, **Yangjin Kim** (Mathematics, Konkuk University)
The role of microenvironment (M1/M2 macrophages) in regulation of cell infiltration in glioblastoma
<http://mbi.osu.edu/event/?id=1136>
28. May 4, 2017, **Adriana Dawes** (Mathematics/Molecular Genetics, Ohio State)
*Phenotypic variability in a mathematical model of *Caenorhabditis vulval* development*
<http://mbi.osu.edu/event/?id=1135>
29. May 9, 2017, **Chuan Xue** (Mathematics, Ohio State)
Derivation of continuum models from individual-based models for chemotaxis of bacterial populations
<http://mbi.osu.edu/event/?id=1133>
30. May 16, 2017, **Xiulan Lai** (Renmin University of China)
Combination therapy of cancer with cancer vaccine and immune checkpoint inhibitors: A mathematical model
<http://mbi.osu.edu/event/?id=1134>

MBI 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 2016-2017 MBI Colloquium speakers were:

1. September 19, 2016, **Michael Shuler** (Biomedical Engineering, Cornell)
Modeling Life
<https://mbi.osu.edu/event/?id=1060>
2. September 21, 2016, **Simon Levin** (Ecology and Evolutionary Biology, Princeton University)

Mathematical Ecology: A Century of Progress, and Challenges for the Next Century
<https://mbi.osu.edu/event/?id=1069>

3. October 26, 2016, **Charles Peskin** (Courant Institute of Mathematical Sciences, New York University)
Fiber Architecture (Differential geometry) of the Heart and its Valves
<https://mbi.osu.edu/event/?id=1070>
4. November 9, 2016, **Elizabeth Thompson** (Statistics, University of Washington)
Finding genes via Relatedness and the Co-ancestry of Genome
<https://mbi.osu.edu/event/?id=1071>
5. December 7, 2016, **Arthur Lander** (Center for Complex Biological Systems, UC Irvine)
Understanding Growth Control
<https://mbi.osu.edu/event/?id=1072>
6. January 11, 2017, **Leah Edelstein-Keshet** (Mathematics, University of British Columbia)
Navigating Biochemical Pathways for Cell Polarization and Motility (A Personal Journey) <https://mbi.osu.edu/event/?id=1111>
7. February 15, 2017, **Joel Cohen** (Populations, Rockefeller and Columbia Universities)
The variation is the theme: Taylor's law from Chagas disease vector control to tornado outbreaks
<https://mbi.osu.edu/event/?id=1112>
8. March 15, 2017, **Uri Alon** (Molecular Cell Biology, Weizmann Institute of Science)
Evolutionary tradeoffs and the geometry of phenotype space
<https://mbi.osu.edu/event/?id=1113>
9. April 12, 2017, **James Keener** (Mathematics, University of Utah)
Cell Physiology: Making Diffusion Your Friend
<https://mbi.osu.edu/event/?id=1114>

PRODUCTS

Publications

Publications in this list are those that appeared in 2016-17 and where the authors explicitly acknowledged MBI in the publication. Such acknowledgment typically arises either by MBI's direct support of the authors (e.g. funded postdocs, long term visitors) or where the authors cite that visiting MBI was an important influence on the publication (e.g. workshops).

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Featured Videos

Videos in this list are those that were created by MBI in 2016-17 for purposes of dissemination, exposure, and advertising of MBI programs. They are housed and available on the MBI website, including on the front page when newly released.

Growth and Morphogenesis – Semester Overview | Philip Maini

2/20/2017

<https://youtu.be/PWSr3tlI3YI>

MBI Visitor Philip Maini gives an overview of the spring 2017 Emphasis Semester on Growth and Morphogenesis.

Mathematics Outreach at COSI | Thomas Woolley

3/10/2017

https://youtu.be/Y_rTAxvmupk

MBI Visitor Thomas Woolley shares his experience using mathematics to conducting science outreach at the Center of Science and Industry (COSI).

Spiraling, Chasing Cells and Zebrafish Patterns | Thomas Woolley

3/10/2017

<https://youtu.be/I6SSIUuwxeM>

MBI Visitor Thomas Woolley explores the way that Zebrafish stripe patterns arise through spiraling cell motion.

The MBI Visitor Program | Kesh Govinder

4/9/2017

<https://youtu.be/gyGjqGAXbQM>

MBI Visitor Kesh Govinder explains the benefits of the MBI Visitor program.

Women Advancing Mathematical Biology

4/25/2017

<https://youtu.be/cENQBZOObVEk>

With support from the Association for Women in Mathematics (AWM), The Society for Mathematical Biology (SMB), and Microsoft Research, MBI hosted Women Advancing Mathematical Biology. The workshop brought a diverse group of women together to conduct new research in the mathematical biosciences and form new collaborations with their peers.

CURRENT BOARD OF TRUSTEES MEMBERS

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Thomas Kurtz (Mathematics and Statistics, University of Wisconsin)

Alan Perelson (Theoretical Biology and Biophysics Group, Los Alamos National Laboratory)

John Reinitz (Departments of Statistics, Institute of Genomics and Systems Biology, University of Chicago)

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Wolfgang Sadec (Internal Medicine, Human Genetics)
Larry Schlesinger (Microbial Infection and Immunity)
R. Keith Slotkin (Molecular Genetics)
Parthasarathy Srinivasan (Computer Science and Engineering, Biomedical Informatics)
Don Stredney (Ohio Supercomputer Center)
Lara Suchestone-Campbell (Pharmacy, Veterinary Biosciences)
Matthew Sullivan (Microbiology)

MBI INSTITUTE PARTNERS IN 2016-2017

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.

MBI currently has 66 Institute Partners, including the withdrawal of Arizona State University and the addition of

1. Cleveland Clinic
2. University of Alaska-Fairbanks
3. University of Pretoria

Continuing Institute Partners:

4. Battelle Memorial Institute
5. Boston University
6. Case Western reserve University
7. Cornell University
8. Drexel University
9. Duke University
10. Florida State University
11. Howard University
12. IBM Corporation
13. Indiana University – Purdue University
14. Instituto Gulbenkian de Cienci

15. Iowa State University
16. Konkuk University
17. Korea University – Sejong Campus
18. McGill University
19. Michigan State University
20. Mississippi State University
21. Moffitt Cancer Center
22. Mount Sinai School of Medicine
23. National Autonomous University of Mexico
24. National Tsing Hua University
25. New Jersey Institute of Technology
26. Ohio University
27. Pennsylvania State University
28. Princeton University
29. Rutgers University at New Brunswick
30. Texas Tech University
31. The Ohio State University
32. Trinity University
33. Tulane University
34. University of Alberta
35. University of Bath
36. University of California, Davis
37. University of California, Irvine
38. University of California, Los Angeles
39. University of California, San Diego
40. University of Chicago
41. University of Cincinnati
42. University of Exeter
43. University of Georgia
44. University of Glasgow
45. University of Houston
46. University of Iowa
47. University of KwaZulu-Natal
48. University of Maryland
49. University of Maryland Baltimore County
50. University of Miami
51. University of Michigan
52. University of Minnesota
53. University of Notre Dame
54. University of Nottingham
55. University of Oxford
56. University of Pittsburgh
57. University of Southern California, Los Angeles
58. University of Twente
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

WORKSHOPS AT INSTITUTE PARTNER'S SITES

From September 1, 2016 – August 31, 2017, MBI helped support one workshop held at MBI partner institutions.

1. **Indiana University-Purdue University**, Department of Mathematical Sciences,
Saturday, February 25, 2017
Fifth Midwest Women in Mathematics Symposium
<http://wims.math.iupui.edu/>

The Fifth Annual Midwest Women in Mathematics Symposium (WIMS) will highlight scholarly contributions of female mathematicians in the Midwest and stimulate collaborations, networking, and mentoring relations among the participants.

Local Organizers

Julia Arciero
Olguta Buse
Joanna Furno

Plenary Speakers

Trachette Jackson (University of Michigan)
Susan Tolman (University of Illinois Urbana-Champaign)

Invited Speakers

Adriana Dawes (Ohio State)
Marisa Eisenberg (University of Michigan)
Tanya Firsova (Kansas State University)
Alexandra Jilkine (University of Notre Dame)
Keiko Kawamuro (University of Iowa)
Laura Schaposnik (University of Illinois Chicago)
Wanda Strychalski (Case Western Reserve University)
Ioana Suvaina (Vanderbilt University)
Anush Tserunyan (University of Illinois Urbana-Champaign)
Liz Vivas (Ohio State)

Colloquium Speaker

Emmy Murphy (Northwestern)

Poster Presenters

Roza Aceska - *Frames in Dynamical Systems*
 Malva Asaad - *Hypoelliptic heat Kernel on Nilpotent Lie Groups*
 Claire Bowen - *Partitioning a Large Simulation as It Runs*
 Margaret Christy - *Quality Control of Blood Sample Analysis for Transplant Patients*
 Sara Clifton - *Handicap principle implies emergence of dimorphic ornaments*
 Willa Del Negro Skeehan - *Staged Progression and Retrogression Model of Influenza*
 Kelsey Dipietro - *Efficient Moving Mesh Methods for Fourth Order PDES*
 Melissa Emory - *Automorphic Representations of GSpin*
 Haixia Li - *A Optimal Subsampling in Generalized Linear Models for Big Data*
 Anh Nguyen - *Perceptual switching in auditory streaming can be understood as an evidence accumulation process*
 Martha Precup - *Singularities of semisimple Hessenberg Varieties*
 Pamela Pyzza - *Temperature Effects on Human Sleep Patterns: A Mathematical Model of Sleep Regulation*
 Marissa Renardy - *A reaction-diffusion model for cell polarization in yeast*
 Vanessa Rivera-Quinones - *Evolutionary branching in disease dynamics*
 Amber Russell - *The Generalized Springer Correspondence*
 Nur Saglam - *Constructions of new Lefschetz fibrations using cyclic group actions*
 Ziting Tang - *A-optimal Weighted Bootstrapping Method and Subsampling in Empirical Likelihood*
 Angela Wei - *Two-Compartment Model of Dopamine Release: Dependence on Firing Pattern*
 Jihyeon Jessie Yang - *Bott Canonical Basis*
 Yue Zhang - *Random Weighting Approach In Nonlinear Regression Models*

PUBLIC LECTURE SERIES 2016-2017

MBI continued to be instrumental in the Science Sundays Public Lecture Series at OSU, including sponsoring a lecture by **Emery Brown**. 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 18, 2016, **Emery Brown**, MD, PhD (Warren M. Zapol Professor of Anesthesia, Massachusetts General Hospital and Harvard Medical School; Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, MIT).
The Rhythms of the Unconscious Brain under General Anesthesia
 No video link available
2. October 23, 2016, **Richard Petty** (Distinguished University Professor, Psychology, Ohio State)
How Confidence Affects Decision Making and Action
https://www.youtube.com/watch?v=884pTRq_6OU
3. November 13, 2016, **Sian Beilock** (Psychology Professor and Director, Human performance Lab, University of Chicago)
How to perform your best under stress
<https://www.youtube.com/watch?v=IelMGL2AtYE>

4. December 4, 2016, **Elisabeth Root**, (Associate Professor, Geography, Ohio State)
Has Cholera Met its Match? Geographic Science and the Fight against a Global Killer
<https://www.youtube.com/watch?v=iL24sUQPZzs&list=PLJqUkHeXIUqdv7RlqV9nlXq17bofXMVTu&index=5>
5. January 22, 2017, **Laura Cadonati** (Associate Professor, Georgia Tech's Center for Relativistic Astrophysics)
Listening to the Universe with Gravitational Waves
<https://www.youtube.com/watch?v=6FaPb6YjJ-E&list=PLJqUkHeXIUqdv7RlqV9nlXq17bofXMVTu&index=3>
6. February 19, 2017, **Matthew Sullivan** (Associate Professor, Microbiology, Ohio State)
Understanding ocean viruses may just save the earth and help cure your next ailment
<https://www.youtube.com/watch?v=E81X0mwLUo0&index=1&list=PLJqUkHeXIUqdv7RlqV9nlXq17bofXMVTu>
7. March 19, 2017, **John Beacom** (Professor, Physics and Astronomy, Ohio State; Director CCAPP)
Neutrino Astronomy Made Easy
<https://youtu.be/L57wn2TJy48>
8. April 23, 2017, **Cara Malek** (Supervises DreamWorks's Character Technology Team)
How Would A Dragon Fly? The Science & Art of Rigging Animated Characters
No video link available

DIVERSITY INITIATIVES

Visiting Lecturer Program

The Visiting Lecturer Program (VLP) sponsors visits of mathematical biologists to institutions that have large numbers of undergraduate students who are members of groups that are under-represented in the mathematical sciences community. The purpose is to encourage members of these groups to go to graduate school and to develop careers in the mathematical biosciences. This program is one of the initiatives suggested by the MBI Diversity Committee.

<http://mbi.osu.edu/education/visiting-lecturer-program/>

The 2016-2017 VLP lectures were:

1. Abdul-Aziz Yakubu, SIDIM 2017 (held this year at University of Puerto Rico - Ponce), March 3-4, 2017
2. Fabio Milner, CeSMUR Conference (held this year at Kansas St University), April 7-8, 2017

MBI Conference Awards

The MBI Conference Award is a full travel award for an untenured junior faculty, postdoc, or graduate student to attend one MBI workshop of the winner's choice. MBI has worked with organizers to set up an evaluation procedure to identify winners at national meetings, including the SACNAS Modern Math Workshop, Blackwell-Tapia Conference, AWM Poster Sessions at JMM and the SIAM Annual Meeting, and NAM's annual Granville-Brown-Hayes Session at JMM. Award winners can be seen at <http://mbi.osu.edu/about/diversity-statement/conference-award-winners/>.

MBI Diversity Workshops

[Spring 2017 CTW Workshop](#) aimed specifically at promoting women and minorities participation in research in math biosciences. See description above.

COMMUNITY INVOLVEMENT IN MBI PROGRAMS

1. ErdosInstitute.org

The Erdős Institute was founded in January of 2017 by a team of scholars from public and private academic institutions.

As leaders of various collaborative interdisciplinary initiatives, we are passionate about building a diverse community of innovative and entrepreneurial academics. We understand the importance of cultivating strong working relationships and connecting talent to resources and opportunities.

By sharing our collaboration tools, programming, and our multi-institutional network of world-class resources, we:

- Facilitate a culture of interdisciplinary collaboration within academia
- Foster collaborations between academics and industry partners
- Turn local collaborations into global solutions

2. Second Workshop on Omics Data Analysis, September 2016

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): about 60 postdocs and junior faculty from different OSU labs/groups attended.

Participants/OSU Departments

Caitlin Slevin, Biomedical Informatics

Wei Meng, Radiation Oncology

Min-Ae Song, Comprehensive Cancer Center

Sean Caruthers, James Molecular Lab

Myrriah Tomar, Comprehensive Cancer Center

Adrienne Dorrance Comprehensive Cancer Center and Internal Medicine

Dukagjin Blakaj, Comprehensive Cancer Center

Eileen Hu, Comprehensive Cancer Center

Jennie Rowell, Nursing

Elizabeth Baskin, Biomedical Informatics

Shannon Gillespie, Nursing

Mohammad Marhabaie, Molecular Genetics

Sushmita Ghoas, Molecular Genetics

Ni Shi, Comprehensive Cancer Center

Satavisha Roy, Comprehensive Cancer Center

Amanda Mitchell, Institute for Behavioral Medicine Research

Saranga Wijeratne, Molecular and Cellular Imaging Center OARDC

Vitor Pavinato, MCIC and Entomology (OARDC/OSU)

Daelynn Buelow, Comprehensive Cancer Center and Pharmacy

Christina Drenberg, Pharmaceutics
 Fabien Habyarimana, Pulmonary, Allergy, Critical Care, and Sleep Medicine
 Curt Walker, College of Medicine
 Kathleen Pishas, Childhood Cancer and Blood Disorders
 Emily Theisen, Childhood Cancer and Blood Disorders
 Ranajeet Saund, Childhood Cancer and Blood Disorders
 Zhongtang Yu, Animal Science
 Mark Weir, Environmental Health Sciences
 Lingling Wang, Animal Sciences
 Katy Lenz, Neuroscience and Psychology
 Eileen Hu, Comprehensive Cancer Center
 Ali Snedden, Battelle Center for Mathematical Medicine, Nationwide Children's
 Yan Wang, Neuroscience
 John Burian, Battelle Center for Mathematical Medicine, Nationwide Children's
 John Ngunjiri, Food Animal Health Research Program – OARDC
 Yu Li, Food Science and Technology
 Nicola Lorenz, Environment and Natural Resources
 Peter Renz, Carbon Management and Sequestration Center
 Jae Yoon Jeon, Pharmacy
 Ola Elgamal, Comprehensive Cancer Center
 Bin Li, Comprehensive Cancer Center
 Susan Grooters, Veterinary Preventive Medicine
 Sara Elgamal, Comprehensive Cancer Center
 Andrew Calinger-Yoak, Preventive Veterinary Medicine
 Yuan Zhang, Nationwide Children's Hospital
 Kevin Ying, Comprehensive Cancer Center
 Mikhail Gavrilin, Internal Medicine
 Jason Benedict, Center for Biostatistics
 Rodolfo Vicetti Miguel, Microbial Infection and Immunity
 Nirk Quispe Calla, Microbial Infection and Immunity
 Kellie Archer, Public Health/Biostatistics
 Melanie Davis, Comprehensive Cancer Center
 Benson Lindsey, Center for Applied Plant Sciences
 Hsiao-chi Chang, EEOB
 Parvathi Ranganathan, Comprehensive Cancer Center
 Lawrence Shirley, Surgery and Comprehensive Cancer Center
 Nick Selner, Comprehensive Cancer Center
 Dalia Elgamal, Comprehensive Cancer Center
 Haidong Yu, Center for Applied Plant Sciences
 Dario Veneziano, Cancer Biology and Genetics
 Jennifer Muszynski, Nationwide Children's Hospital

3. Clinical Trials 2-day workshop, May 2017

Faculty from the Statistics Department, the Division of Biostatistics (College of Public Health) taught and developed modules for this workshop: about 30 participants (clinicians and research scientists)

Participants/OSU Departments

Omar Hussein, Neurology
Jessica Wobb, Radiation Oncology
Sagar Sardesai, Medical Oncology
Junan Li, Pharmacy
Dwight Owen, Medical Oncology
Carolina Ricco, Veterinary Medicine
Eric Miller, Radiation Oncology
Emma Warry, Veterinary Medicine, Clinical Sciences
Vincent Wavreille, Veterinary Biosciences
Joelle Fenger, Veterinary Clinical Sciences
Carmen Cantemir-Stone, Biomedical Informatics
Marilly Palettas, Biomedical Informatics
Songzhu Zhao, Biomedical Informatics
Jason Benedict, Biomedical Informatics
Samir Acharya, Cancer Biology and Genetics
Juan Peng, Biomedical Informatics
Brett Klamer, Biomedical Informatics
Jeff Gaither, Mathematical Biosciences Institute
RB McGee, MBI/BMI
Farrah Sadre-Marandi, Mathematical Biosciences Institute
Jennifer Muszynski, Pediatrics
Kun Huang, Biomedical Informatics
Juan Huang, Optometry
Raju Raval, Radiation Oncology
Ying Huang, Hematology
Akwasi Agyeman, Hematology
QiuHong Zhao, Hematology
Mirela Anghelina, Hematology
Shikha Wadhwani, DOIM/Nephrology

4. JKTG Foundation Cancer Group May 18-21, 2017

Applied Mathematics in Germinating Oncology Solutions (AMIGOS) group members and a few new participants* met Fri. May 18-Sunday May 21 to discuss clinical challenges and fundamental concepts in oncology. The event was partially supported by the Jayne Koskinas Ted Giovanis (JKTG) Foundation and the Breast Cancer Research Foundation.

Attendees:

Ronald Chen* (Radiation Oncology, UNC School of Medicine)
Tom Chou (Depts. Of Biomathematics and Mathematics, UCLA)
Heiko Enderling (Moffitt Cancer Center)
Christos Hatzis (Yale Cancer Center)
Russell Rockne (Mathematical Oncology, City of Hope)
Blerta Shtylla* (Dept. of Mathematics, Pomona College)
Andrew Wang (Radiation Oncology, UNC School of Medicine)

Leo Wang* (Dept. of Immuno-Oncology, City of Hope)
Meng Welliver* (Radiation Oncology, Ohio State University)

Topics discussed:

- **RT induced bladder/rectum acute toxicity.**

Rationale: Almost 200,000 men are diagnosed with prostate cancer in the US each year, and about ½ of these men will receive radiation therapy with curative intent. Patients who undergo radiation therapy for prostate cancer suffer toxicity from radiation damage to the bladder and rectum. This toxicity diminished quality of life of PC patients. Understanding the doses of radiation to bladder and rectum which cause these damages and toxicities is essential to knowing how to better design radiation treatment to minimize toxicity and patient suffering.

Background: Radiation planning for each patient begins with a CT scan, and the physician then demarcates the prostate (radiation target) and the adjacent organs (bladder and rectum). Radiation treatment can be given from up to 360 angles around the patient's body, and there are innumerable ways to use these angles and beam energies to design radiation plans which deliver different doses to the different structures. It is surprising that the relationship between how much dose is delivered to these organs (bladder and rectum) and the probability and severity of toxicity (urinary and bowel) is not well-understood.

We have three-dimensional anatomical dose data for 400 patients. These same patients answered questionnaires on the following symptoms are available for each patient before starting radiation treatment, and weekly during treatment:

Urination: frequency, nighttime urination, urgency, leakage, burning with urination, bladder spasms, ease of flow.

Rectum/bowel: diarrhea, blood in stool, urgency, feeling a need to have bowel movement but nothing passes, leakage.

We have also collected each patient's age, race, prostate cancer stage and other diagnostic details.

- Aim 1: Implement a correlative study between questionnaire answers and radiation doses. Instead of simply looking at the dose-volume histogram (DVH), we will stratify the patients and correlate the scores from the 12 questions with their full spatial radiation dosage. The correlation will be validated using a training subset of patient data.
- Aim 2: We will construct a new, spatially dependent objective function that penalizes radiation in the areas that correlate with diminished urinary quality of life.
- Aim 3: The new objective function will be incorporated as an additional constraint into the beam shaping algorithm. The new radiation dosing profiles will be optimized with the additional constraint imposed by outcome of quality of life. These new dosage patterns will be tested on new patients.

- **Predicting optimal drug dose/scheduling for individual TNBC patients**

TNBC exhibits inter-patient heterogeneity in response to drug cocktails, with evolving resistance that is difficult to predict. Thus there is a need to 1) understand evolutionary dynamics during therapy and identify evolutionary trajectories of developing or pre-existing resistant subclones; and 2) identify best drug dose/scheduling to personalize TNBC therapy and improve outcomes.

Since there are an infinite number of drug dose/schedule combinations,

- Aim 1. Barcoding. Identify clones developing/evolving during Crizo/ABT in MDA-MB 231.
- Aim 2. Develop a mathematical model of clonal TNBC growth and response to Crizo and ABT. Calibrate the model with experimental data of IC_{0-100} and different combinations for MDA-MB 231. Calculate optimal dose/schedule to control (burden/time) tumor. Validate experimentally *in vitro*.
- Aim 3. Derive IC_{0-100} for Crizo/ABT for cell lines. Predict optimal dose/schedule for cell lines. Validate experimentally *in vitro*.
- Future work: Validate framework *in vivo*. Future: replace cell line with patient-specific sample. Use model to predict patient-specific optimal drug dose/schedule.

- **Drug and RT combinations for Head and Neck Cancer.**

Background: Several chemotherapy regimens are known to be synergistic with radiation in head and neck cancer. Cisplatin, cetuximab, carboplatin and taxol are all standard regimens and the chemotherapy agents have different mechanism of action. However, there is no "mix" chemoradiation regimen--ie, cisplatin one week, cetuximab next week etc. Hypothesis: Chemoradiation regimens with mix of agents can be more effective than "pure" regimens

- Aim 1: establish models that fit response of existing "pure regimens." Use existing clinical data?
- Aim 2: Experimentally (in vitro and in vivo) determine the interaction of different drug regimens.
- Aim 3: Use above information to examine whether mixed regimens can be more effective and to optimize mixed regimens. Motivate combining linear-quadratic models with dose models?

- **Mathematical/modeling concepts/questions discussed:**

- **Benefit of multidrug combinations?** Arising from discussions of topics 2 and 3 above, the modeling question arose: What kind of benefit might be expected for simultaneous drug treatment of heterogeneous or evolving tumors? Is there a structural similarity with the relatively well-characterized concepts used to motivate multi-drug cocktails in HIV treatment? Possible mathematical approaches to answer these questions include understanding the basic mechanisms of drug action, mapping phenotypic heterogeneity into drug susceptibility space, and developing stochastic models of escape and evolution.
- **Keystone species?** Are the dynamics of heterogeneous tumors reliant on only a small number of clones? There is a possible connection with ideals from ecology in which there

are often “keystone species” upon which very few species govern the large viability of the entire ecosystem. Such an effect may arise from statistical connectivity properties of the network (e.g., food web) and the heterogeneous magnitudes of the interactions. What methods can be used to detect and identify such keystone species, and what design principles lead to such structure? Identifying the important players in tumor evolution can have implications for development of targeted therapeutics.

- **Antigen evolution and immune response.** Search for principles governing immune response in the context of the Abscopal effect. For example, can TCR diversity of activated T-cells be maintained or increased by upregulating IL-2 via immune response to one tumor stimulate T-cells with other TCRs that recognize other tumors within the organism? What level of control can be exerted on the immune system to maximize T-cell diversity and/or mitigate effects of regulatory T-cells?
- **Chemical Abstracts** The Technology Commercialization Office (TCO) put together a 1-day meeting between Chemical Abstracts Services (CAS), TCO, and representatives from MBI and OSU's Data Analytics Initiative. This meeting served to expose and educate each other on various needs and skill sets that could be blended together to do research and solve problems for all parties involved. Future meetings and hopefully future collaborative projects are expected.

5. ASC Commercialization Summit

The College of Arts&Sciences (ASC) hosted a one-day Commercialization Summit at MBI for OSU researchers (including representatives from MBI) to meet and learn about the numerous interactions OSU researchers have had with Industry and Commercialization. Seventeen presentations were made to 30-35 people, with breaks and time for questions.

Agenda

7:30 a.m. Continental breakfast meet and greet (breakfast set at 8:00)		
	Speaker	Department
8:30 a.m. Opening remarks	Christopher Hadad	College of Arts and Sciences
8:35 a.m. Opening remarks	Matt McNair	Corporate Engagement Office
8:45 a.m. Keynote address	Jon Parquette	Chemistry and Biochemistry
9:20 a.m. Presentation	Chris Hammel	Physics
9:40 a.m. Presentation	Marie-Catherine de Marneffe	Linguistics
10:00 a.m. Presentation	Roman Holowsky	Mathematics
10:20 a.m. Break		
10:40 a.m. Presentation	Dongbin Xiu	Mathematics
11:00 a.m. Presentation	Eric Bielefeld	Speech and Hearing
11:20 a.m. Presentation	Keith Slotkin	Molecular Genetics
11:40 a.m. Presentation	Abraham Badu-Tawiah	Chemistry and Biochemistry
12:00 p.m. Lunch break		
1:00 p.m. Presentation	Art Gooray	Technology Commercialization Office
1:20 p.m. Presentation	Sandy Shew/Michael Hardesty	ASCTech
1:40 p.m. Presentation	Steve Petrill	Psychology
2:00 p.m. Presentation	Anne Co	Chemistry and Biochemistry
2:20 p.m. Break		
2:40 p.m. Presentation	Jay Hollick	Molecular Genetics
3:00 p.m. Presentation	Robert Baker	Chemistry and Biochemistry
3:20 p.m. Presentation	Jim Fowler/Bart Snapp	Mathematics
3:40 p.m. Presentation	Michael White	Linguistics
4:00 p.m. Presentation	Christopher Hadad	Chemistry and Biochemistry
4:30 p.m. Reception		

6. Co-sponsored postdocs and visitors that were partially supported by MBI

- **Min Wang** – Postdoctoral Fellow
- **Reginald McGee** – Postdoctoral Fellow
- **Maciej Pietrzak** – Postdoctoral Fellow
- **Ben Fogelson** – Postdoctoral Researcher
- **Xiulan Lai** – Long Term Visitor
- **Yury Puerta** – Long Term Visitor

EXTERNAL EVALUATION OF MBI

MBI has a contract with Strategic Research Group (<http://www.strategicresearchgroup.com/index.htm>) to perform an independent evaluation of MBI programming based on online questionnaires and personal interviews.

PROGRAM INITIATIVES

2017-2018 Emphasis Programs

The theme for the **Autumn 2017 Emphasis program** is *Control in Biology and Medicine*.

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 will focus 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 will be on the control and modulation of neuronal and motor systems. This includes the study of rhythmic activity patterns in the brain that underlie essential functions such locomotion, respiration, and circadian activity, or which arise in pathological situations such as epilepsy and Parkinson's disease. The workshop will also encompass control of non-oscillatory motor behaviors such as maintaining posture and generating specialized non-repetitive movements.
- Workshop 2 will be on the control of cellular and molecular systems. This includes the use of control theory to understand and modulate gene expression and cell signaling. It

will also consider synthetic biology, which is the design of cellular regulatory systems to accomplish desired outcomes.

- Workshop 3 will be on the control of disease using personalized medicine. This will address how control theory, particularly system identification and robust control, can be used to overcome the challenges of designing drug- and device-based medical treatments given the individual variability within a patient population.
- Workshop 4 will be 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 will be attended by researchers studying humans and non-human animals and those that try to build robots, performing movements of different types.

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

Organizing Committee

- **German Enciso**, Mathematics, UC Irvine
- **Pablo Iglesias**, Electrical and Computer Engineering, Johns Hopkins University
- **Jeff Moehlis**, Mechanical Engineering, UC Santa Barbara
- **Mette Olufsen**, Mathematics, NC State University
- **Jonathan Rubin**, Mathematics, University of Pittsburgh
- **Peter Thomas**, Mathematics, Applied Mathematics, and Statistics, Case Western Reserve University

Planned Workshops for Autumn Semester 2017

1. *Control and Modulation of Neuronal and Motor Systems* (September 11-15, 2017)
2. *Control of Cellular and Molecular Systems* (October 2-6, 2017)
3. *Control of Disease: Personalized Medicine Across Heterogeneous Populations* (October 30 – November 3, 2017)
4. *Sensori-motor control of animals and robots* (November 13-17, 2017)

The theme for the **Spring 2018 Emphasis Program** is *Infectious Diseases: Data, Modeling, Decisions*.

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 adapt and evolve, 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 will consist of four workshops focusing at the crucial areas of modeling modern infectious diseases born.

Organizing Committee

- **Carlos Castillo-Chavez**, MCMSC, Arizona State University
- **Caroyln Cho**, Quantitative Pharmacology and Pharmacometrics, Merck, Sharp, and 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, Ohio State University
- **Joe Tien**, Mathematics, Ohio State
- **Pauline van den Driessche**, Mathematics and Statistics, University of Victoria

Planned Workshops for Spring Semester 2018

1. *Host-Pathogen Dynamics* (February 19-23, 2018)
2. *Socioepidemiology* (March 5-9, 2018)

3. *Disease Ecology/Eco-epidemiology* (March 26 – March 30, 2018)
4. *Multiscale Dynamics of Infections* (April 23 – 27, 2018)