Annual Report for DMS-1440386
For Year 2015-2016

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 2015-2016:

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 which 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 will pursue 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 2015-2016

MBI hosted two Emphasis Semester programs in 2015-2016: the Autumn 2015 Emphasis Semester was on *Mathematical Molecular Biosciences* and the Spring 2016 semester was on *Dynamics of Biologically Inspired Networks*.

The Organizing Committee for the **Autumn 2015 Semester** consisted of **Emil Alexov** (Computational Biophysics and Bioinformatics, Clemson University), **Ridgway Scott** (Computer Science and Mathematics, University of Chicago), **Reidun Twarock** (Mathematics and Biology, University of York), and **Guowei Wei** (Mathematics, Michigan State University).

This one-semester program brought together researchers from mathematics, chemistry, physics, biology, computer science, and engineering to explore new ways to bridge these diverse disciplines, and to facilitate the use of mathematics to solve open problems at the forefront of the molecular biosciences.

With the availability of modern biotechnologies, an important trend in traditional life sciences disciplines (such as physiology, plant biology, neuroscience etc.) is a fundamental transition from macroscopic phenomenological disciplines to molecular based biosciences ones. In parallel with this development, a major change in the life sciences in the 21st century is the transformation to quantitative and predictive sciences. Revolutionary opportunities have emerged for mathematically driven advances in biological research. In the past few decades experimental exploration of self-organizing molecular biological systems (such as HIV viruses, molecular motors and proteins in

Alzheimer's disease) are examples of dominating driving forces in scientific discovery and innovation. However, the emergence of excessive complexity in self-organizing biological systems poses fundamental challenges to their quantitative description, because of the excessively high dimensionality and the complexity of the processes involved. Mathematical approaches that are able to efficiently reduce the number of degrees of freedom, and model complex biological systems, are becoming increasingly popular in molecular biosciences. Multiscale modeling, manifold extraction, dimensionality reduction and machine learning techniques have been introduced to reduce the complexity of biomolecular systems while maintaining an essential and adequate description of the biomolecules of interest.

Currently, a major barrier for mathematical scientists to work in this field is the lack of knowledge in molecular biology, while a major barrier for biologists is the lack of knowledge about modern mathematical tools and techniques that have been developed in the past 20 years. This semester workshop program was designed to help bridge gaps between molecular biologists and mathematical scientists and to facilitate their collaborations. There is enormous potential in this area for integrative interdisciplinary research in which theoreticians and experimentalists develop solutions to challenging problems in tandem. This program acted as a catalyst to exploit these synergies and to create a network of collaborations that will sustain future activities in this area beyond the duration of this program.

Autumn 2015 Emphasis Semester Workshops

1. Workshop on Omics Data Analysis (September 16-18, 2015)
2. Workshop 1: Geometric and Topological Modeling of Biomolecules (Sept 28 – Oct 2, 2015)
3. Workshop 2: Multiple Faces of Biomolecular Electrostatics (Oct 12-16, 2015)
4. Workshop 3: Modeling and Computation of Transmembrane Transport (November 16-20, 2015)
5. Workshop 4: Mathematical Challenges in Drug & Protein Design (Dec 7-11, 2015)

Autumn 2015 Current Topic Workshops

1. Uncertainty, Sensitivity and Predictability in Ecology: Mathematical Challenges and Ecological Applications (October 26-30, 2015)
2. Foundations Meet Translation (December 2, 2015)

The Organizing Committee for the **Spring 2016 Emphasis Semester** on *Dynamics of Biologically Inspired Networks* consisted of **Pete Ashwin** (College of Engineering, Mathematics and Physical Sciences, University of Exeter), **Nina Fefferman** (Ecology and Evolutionary Biology, University of Tennessee), **Martin Feinberg** (Chemical Engineering & Mathematics, The Ohio State University), **Leon Glass** (Department of Physiology, McGill University, Macdonald Campus), **Adilson Motter** (Physics, Northwestern University), **Mason Porter** (Mathematical Institute, University of Oxford), and **Ruth Williams** (Mathematics, University of California, San Diego).

The MBI network program is part of a yearlong cooperative program with IMA. To see the fall 2015 IMA network workshops go to http://www.ima.umn.edu/2015-2016/ima-mbi-program.html.

Networks and deterministic and stochastic dynamical systems on networks are used as models in many areas of biology. This underscores the importance of developing tools to understand the interplay between network structures and dynamical processes, as well as how network dynamics can be controlled. The dynamics associated with such models are often different from what one might traditionally expect from a large system of equations, and these differences present the opportunity to develop exciting new theories and methods that should facilitate the analysis of specific models. Moreover, a nascent area of research is the dynamics of networks in which the networks themselves change in time, which occurs, for example, in plasticity in neuroscience and in up regulation and down regulation of enzymes in biochemical systems.

There are many areas in biology (including neuroscience, gene networks, and epidemiology) in which network analysis is now standard. Techniques from network science have yielded many biological insights in these fields and their study has yielded many theorems. Moreover, these areas continue to be exciting areas that contain both concrete and general mathematical problems. Workshop 1 explores the mathematics behind the applications in which restrictions on general coupled systems are important. Examples of such restrictions include symmetry, Boolean dynamics, and mass-action kinetics; and each of these special properties permits the proof of theorems about dynamics on these special networks.

Workshop 2 focuses on the interplay between stochastic and deterministic behavior in biological networks. An important related problem is to understand how stochasticity affects parameter estimation. Analyzing the relationship between stochastic changes, network structure, and network dynamics poses mathematical questions that are new, difficult, and fascinating.

In recent years, an increasing number of biological systems have been modeled using networks whose structure changes in time or which use multiple kinds of couplings between the same nodes or couplings that are not just pairwise. General theories such as groupoids and hypergraphs have been developed to handle the structure in some of these more general coupled systems, and specific application models have been studied by simulation. Workshop 3 will bring together theorists, modelers, and experimentalists to address the modeling of biological systems using new network structures and the analysis of such structures.

Biological systems use control to achieve desired dynamics and prevent undesirable behaviors. Consequently, the study of network control is important both to reveal naturally evolved control mechanisms that underlie the functioning of biological systems and to develop human-designed control interventions to recover lost function, mitigate failures, or repurpose biological networks. Workshop 4 will address the challenging subjects of control and observability of network dynamics.

Spring 2016 Emphasis Semester Workshops

1. Workshop 1: Dynamics in Networks with Special Properties (Jan 25-29, 2016)
2. Workshop 2: The Interplay of Stochastic and Deterministic Dynamics in Networks (Feb 22-26, 2016)
3. Workshop 3: Generalized Network Structures and Dynamics (Mar 21-15, 2016)
4. Workshop 4: Control and Observability of Network Dynamics (Apr 11-15, 2016)

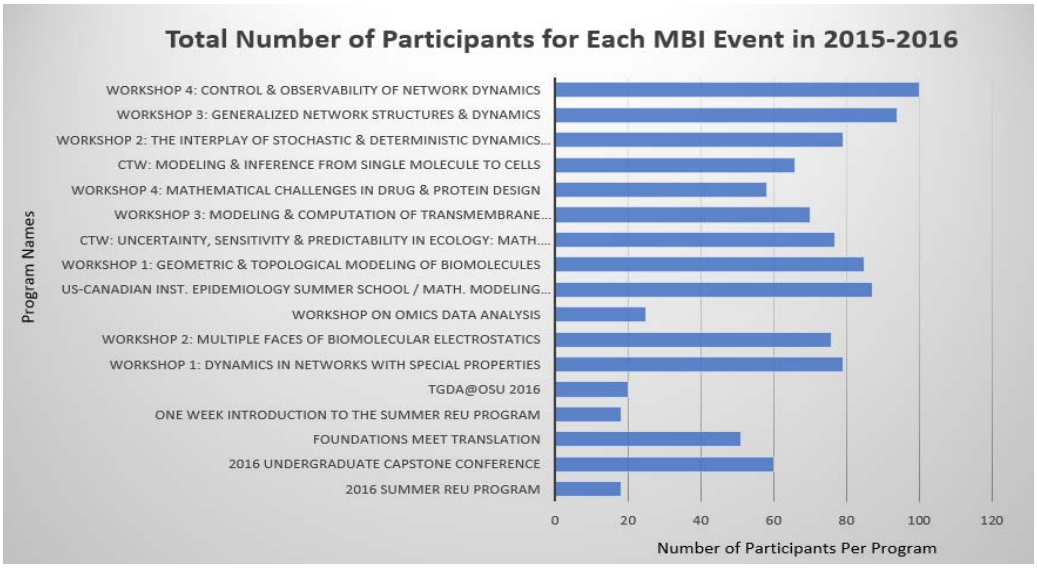
Spring 2016 Current Topic Workshops

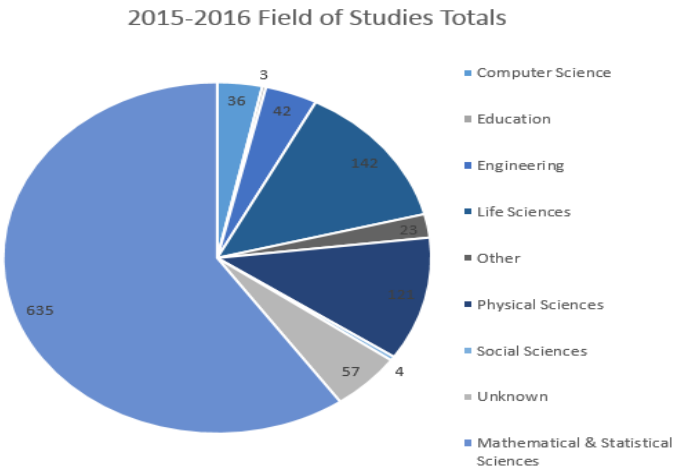
Modeling and Inference from Single Molecules to Cells (Feb 8-12, 2016)

Participant Data

A complete list of participant data is attached in the Participant/Organization section of the research.gov online reporting form.

1147 participants took part in MBI's 2015-2016 Workshop Programs.





MBI WORKSHOP REPORTS

Autumn Workshop 1 - Geometric and Topological Modeling of Biomolecules (Sept. 28 – Oct. 2, 2015)

Organizers: Christine Heitsch (Georgia Institute of Technology), Karin Musier-Forsyth (Ohio State University), Reidun Twarock (University of York), Alexander Vologodskii (New York University)

Report by: Guang Lin, Matthew Oremland, Farrah Sadre-Marandi

MONDAY, SEPTEMBER 28, 2015

Landau theories of the assembly of a virus
Robijn Bruinsma (University of California, Los Angeles)
A new approach to the capsid structures of small viruses with icosahedral symmetry was proposed. It generalizes the Landau-Brazovskii theory, which predicts the BCC phase and solidification, to describe icosahedral viral shells self-assembled from identical asymmetric proteins. This explicit characterization was then compared to previous work by Lorman and Rochal. The authors arrived at the conclusion that there should be no activation energy barrier, even though earlier models conflict with this result. When their work was extended, they found their result is a special case of a general family of theories for assembly on icosahedral shells with broken chiral symmetry. This talk presented a new theory which describes in a uniform way both the structures satisfying the Lorman and Rochal geometrical model for capsid construction and those violating it. The extended Landau theory is able to describe the two cases: odd L implying the classical model with no activation energy barrier, and even L which always has a free energy activation energy barrier.

Self-tightening knots: Are they real or not?
Alexander Grosberg (New York University)
Knots are encountered in virtually every branch of physics, supplying physicists and mathematicians with excellent problems to investigate for one and a half centuries. In a more specific context, knotted DNA has been at the center of attention for over three decades. This talk gave an overview of recent research on self-tightening DNA knots and brought awareness of many simple basic questions that remain unanswered. For instance, the most fundamental physical property of any macromolecule - its average size R(N), scaling with chain length N, and depending on the solvent conditions - is not understood for knotted polymers. While everyday experience suggests that knots are very common in long linear strings of any kind, and they get quite tight whenever a string is not carefully handled, the study of knots in polymers concentrated almost exclusively on closed loops. However, if the string is long enough, while the knot occupies a short fragment of it far from the ends, then distinguishing between different knots, or between knots and no knots, becomes sufficiently unambiguous. The question if the knots in DNA are tight or spread remains unanswered.

Rigidity and flexibility of larger molecular structures: Mathematical and computational challenges

Ileana Streinu (Smith College)

Biological macromolecules, such as proteins, are flexible structures held together by a variety of stabilizing interactions. This brings to question the rigidity and flexibility of these molecules, and the answers may reveal intrinsic biological functions or unusual properties. Several methods that shed light on these questions are surveyed. A new systematic rigidity-based method for simulating slow-motion conformational changes in biomolecules in proposed. The essence of this approach is a dimension reduction of the conformational space. To test and experiment these ideas, a new software by Streinu's group, called KINARI, was developed. This software generated kinematically-realistic motions of biological macromolecules with better accuracy and speed. Though challenges occur when using biological data from The Protein Databank (PDB) and the Open Crystallography Database (COD) since this data is full of noise.

Persistent homology analysis of big data in biomolecules

Kelin Xia (Michigan State University)

Persistent homology has emerged as a popular technique for the topological simplification of big data, including biomolecular data. This data has different patterns and shapes, which can be used to predict functions by structure. Yet viruses, for instance, have millions of atoms which lead to a challenging analysis. Persistent homology has been introduced for extracting molecular topological fingerprints based on the persistence of the molecular topological invariants. Since topological tools incur too much reduction, persistent homology bridges the gap between geometry and topology. An accumulated bar length generated from persistent topological invariants for the quantitative modeling of protein flexibility is proposed. The molecular topological fingerprints are also able to characterize topological evolution during protein folding.

Assembly of ssRNA Viruses I: Identification of packaging signals and their role in assembly

Eric Dykeman (University of York)

Multiple dispersed sequence/structure motifs in single-stranded RNA genomes termed packaging signals have been shown to play crucial roles in virus assembly. Theoretical tools for these packaging signals can be applied to a wide range of single-stranded RNA (ssRNA), enabling analysis and investigation into the assembly of the viruses. In terms of assembly, efficiency is focused on as the main metric for packaging signals, although ideas related to selective genome packaging are discussed as well. A variety of models are presented showing differences in effect on assembly, and the implications for each is discussed. Generally speaking, the models that emphasize efficiency are more reliable. We show that graph theoretical tools can be used to better understand the complexity of the assembly process. Several statistical and analytical tools are applied to this process, illustrating how models of packaging signals can be built, analyzed, and in particular, how they can be useful in understanding single-stranded RNA assembly.

Assembly of ssRNA viruses II: Consequences of Packaging Signal Mediated Assembly for Viral Evolution
Reidun Twarock (University of York)
This talk is a follow-up to that of Eric Dykeman, and expands on the investigation of packaging signals in single-stranded RNA viruses. While the previous talk had focused on efficiency, this talk focuses more on how packaging signals play into the evolution of viruses; in particular, how viral evolution is sometimes hindered by packaging signals.
Packaging signals provide an instruction manual for efficient virus assembly and thus place constraints on the evolution of single-stranded RNA genomes. The evolutionary dynamics of single-stranded viruses occur on a fitness landscape that is affected by packaging signal mediation. The geometry of the fitness landscape contains insights into the interplay between the role of packaging signals on both the assembly and the evolution of viruses. Finally, the consequences of viral geometry for evolution are presented and discussed, highlighting the importance of packaging signal mediation.

Sticky spheres: toward a theory of self-assembly
Miranda Holmes-Cerfon (Courant Institute)
Macroscopic structures of materials are dependent on the 'building blocks' of which they consist. How does self-assembly happen, particularly in the case of colloids, and can this be re-created as an inverse problem? Small clusters have been shown to give rise to a wide variety of macroscopic structures. Understanding this process requires knowledge of free energy and kinetics. At the particle level, free energy only has an effect at short range. The geometrical landscape consists of manifolds depending on the arrangement of the particles. The 'sticky parameter' determines how potential energy should be measured when potential is very short-ranged. In fact, it gives rise to a geometric partition landscape. With 6 sticky spheres, two-dimensional manifolds can be explicitly determined, and Monte Carlo schemes can be applied for higher dimensions. Similar calculations can be carried out for discs in the 2D plane.

The question of kinetics can be thought of in terms of transitions from one rigid structure to another. Transition path theory can be used to determine transition rates, and the required PDEs can be reduced to a combination of ODEs and transition paths. Varying parameters and experimental design in these models allows exploration of the nature of self-assembly, though the computations are not trivial.

Predicting the geometry of self-assembling nanoparticles
Giuliana Indelicato (University of Torino)
Many self-assembled structures are observed at the nanoparticle scale, and they vary in shape and function. Structures of proteins often have a very specific purpose that is enhanced by their form. What are the symmetric structures that can occur as a result of self-assembly? There are a number of steps in answering this question. It is first necessary to determine the topology of the structures; this can be done using techniques from planar graph theory. The second step is to limit the search to symmetrical topologies; for example, tetrahedral, octahedral, and icosahedral symmetries. The third step is to superimpose the graph onto a planar lattice. Next, the vertices are superimposed uniformly on the surface

of a sphere. After following this process, several structures emerge with similar construction. Further ongoing work attempts to extend this analysis to elongated structures.

TUESDAY, SEPTEMBER 29, 2015

The decision to assemble: A molecular switch governing HIV-1 particle assembly
Alan Rein (National Institutes of Health)
The assembly of retroviral particles is mediated by the Gag protein, and the expression of this protein in mammalian cells is sufficient for efficient assembly of virus particles in vivo and in vitro for virus-like particles (VLPs). VLP assembly is mediated largely by interactions between the capsid (CA) domains of Gag molecules but is facilitated by the binding of the nucleocapsid (NC) domain to the nucleic acid. Two questions arise: what is the role of RNA during the assembly, and even more, is RNA necessary for assembly? To answer these questions, the talk focuses on the SP1 region of Gag, which lies between the CA domain and the NC domain.
It is found that the SP1 region of HIV-1 Gag is absolutely crucial for VLP assembly and is proposed to form a six-helix bundle in assembled virions. In fact, immature particle assembly by HIV-1 Gag is extraordinarily sensitive to changes in the first ~6 residues of SP1. This leads to the conclusion that the SP1 domain in HIV, which is clearly capable of assuming alternative conformations, acts as a switch whose structure changes when the C-terminal region of Gag oligomerizes.

Structural Basis for the Mature HIV-1 Capsid Assembly
Peijun Zhang (University of Pittsburgh)
Retroviral capsid proteins are conserved structurally but assembly into different morphologies. The HIV-1 capsid is best described by a fullerene cone model, in which hexamers of the capsid protein are linked to form a hexagonal surface lattice that is closed by incorporating 12 capsid protein pentamers. This conical structure and assembly is analyzed using 3D cryo-electron microscopy (cryoEM). It is found that the pentamers and hexamers are held together entirely through CA CTD-CTD dimer and trimer interactions. The dimer interfaces are variable, thus providing plasticity for the asymmetric, curved assembly. A tighter trimer interface is required for pentamer incorporation and thus generating the curvature and capsid closure. Lastly, the host cell factor CypA stabilizes and protects the mature capsid assembly through a second non-canonical interaction site.

Self-assembly of mature conical HIV particles: The role of membrane and genome
Roya Zandi (University of California, Riverside)
The RNA genome of retroviruses is encased within a protein capsid. Most viruses adopt spherical capsid shapes, but the HIV-1 mature capsid assembles into conical shapes, each with different sizes and number of molecules. To gather insight into the assembly and function of this capsid, electron cryotomography has been used though no consensus has been formed. Two models for maturation are proposed. First the full-disassembly of the immature lattice after proteolysis is followed by de novo reassembly of a mature CA lattice as the conical-shaped core. Second, the transformation of the immature lattice into the mature conical capsid is done without full-disassembly.

To study the impact of the RNA and membrane in the assembly process, a new model is proposed and analyzed. It is shown that the presence of the membrane restricts the capsid growth and induces a stress large enough to force the conical shape. In addition, the model without binding to the RNA shows an unlikely event with the RNA being pushed out of the capsid. Both of these results emphasize the importance of the RNA and membrane in the assembly of mature HIV-1 conical capsids.

Deciphering chromatin organization from modeling and experiment
Tamar Schlick (New York University)
The structure of chromatin is crucial to the regulation of eukaryotic cells, such as determining gene activity, cell cycle stage, and DNA replication and repair. The chromatin state depends on many factors including DNA linker length, nucleosome positioning, linker histone concentration, histone variants, and PTMs. Yet, the structure of chromatin remains unknown and controversial. In this talk, recent advances in chromatin modeling techniques were presented with a view toward developing multiscale computational strategies to integrate such findings. A combination of coarse-grain modeling and large-scale all-atom molecular dynamics simulations was shown to yield new results. A mesoscale chromatin model, enhances for long fiber simulations, suggest with cross-linking data a hierarchical-looping model for metaphase chromosomes. Mutliscale simulations (atomistic to mesoscale) also suggest a new mechanism of fiber unfolding nu H4K16 acetylation. This work opens new avenues for other multiscale studies of nuclear processes to bridge spatial and temporal gaps.

Quantitative modeling of nucleic-acid protein interactions
Ralf Bundschuh (Ohio State University)
RNA protein interactions control the fate of cellular RNAs and play an important role in gene regulation, structure, and prediction. An interdependency between such interactions allows for the implementation of logic functions in gene regulation. The interplay between RNA binding partners is investigated, in three stages. First, with perfect sequence specificity, it is assumed one protein can bind to only one designated spot on the RNA. Second, to make it more realistic, this model is extended to assume there are multiple binding sites. This model yields a better correlation and RNA complete data without needing to take into account the structure. Lastly the third model proposed assumes two proteins with protein-protein cooperativity between binding events due to the secondary structure of RNA. The interplay between the RNA binding partners is investigated in the context of statistical physics and a linear correlation function between the two partners as a measurement of the interdependency of their binding events is defined. The emergence of a long-range power-law behavior of this linear correlation function is demonstrated. This suggests the RNA secondary structure driven interdependency between binding sites is a general mechanism for combinatorial post-transcriptional gene regulation.

Automation of RNA 3D motif identification, extraction, and clustering
Neocles Leontis (Bowling Green State University)
The analysis of atomic-resolution RNA 3D structures reveals that many internal and hairpin loops are modular, recurrent, and structured by conserved non-Watson-Crick base

pairs. Although usually drawn as single-strand "loops" in RNA 2D diagrams, recurrent motifs share a common 3D structure, but can vary in sequence. To further the understanding of RNA motif structure and sequence variability, a new tool called the RNA 3D Motif Atlas is presented. The goal is to classify new RNA structure, update non-redundant sets of 3D structures, and update probabilistic models for 3D motif prediction. To classify the motif instances, a representative set of internal and hairpin loops is automatically extracted from a non-redundant list of RNA-containing PDB files. Their structures are compared geometrically, all-against-all, using the FR3D program suite. The loops are clustered into motif groups, taking into account geometric similarity and structural annotations and making allowance for a variable number of bulged bases. The RNA 3D Motif Atlas provides an interactive user interface for exploring motif diversity and tools for programmatic data access.

Structural insights into retroviral RNA genomes
Karin Musier-Forsyth (Ohio State University)
Retroviral replication and assembly is a large area of research with the drive to create novel assembly inhibitor treatments for HIV-1 patients. A complete understanding of the mechanisms controlling retroviral replication requires structural characterization of the RNA, though the HIV-1 genome is extremely complex. Previous efforts to characterize the 3D structure of the HIV-1 RNA have employed a variety of techniques including mass spectrometry, Förster resonance energy transfer, and small-angle X-ray scattering (SAXS) to generate lower-resolution structural models. A new combination of techniques to characterize RNAs is presented where SAXS is coupled with computation molecular modeling and structure probing. Similarities and differences are discussed.

WEDNESDAY, SEPTEMBER 30, 2015

Topological Complexity in Protein Structures
Erica Flapan (Pomona College)
For DNA molecules, topological complexity occurs exclusively as the result of knotting or linking of the polynucleotide backbone. In 1994, Liang and Mislow identified protein contains knots. Based on William R. Talor's theory, knots occur because one terminus threads through a twisted hairpin. The definition of the unknotting number is the smallest number of crossings that must be changed in a knot to obtain the unknot. A few knots and links have been found within the polypeptide backbones of some protein structures. However, non-planarity can also result from the connectivity between a polypeptide chain and inter- and intra-chain linking via cofactors and disulfide bonds.

In this talk, the known types of knots, links, and non-planar graphs in protein structures with and without including such bonds and cofactors are discussed. Several examples of protein structures ontaining Mobius ladders and other non-planar graphs as a result of these cofactors were discussed. The most common type of protein links are Hopf links. In 1995 Liang and Mislow identified this protein link in cytochrome c_3 from Desulfovibrio vulgarism Miyazaki.

Finally, hypothetical structures are proposed that illustrate specific disulfide connectivities that would result in the key ring link, the Whitehead link and the 51 knot. The chainmail protein link is a capsid that protects the virus bacteriophage HK97. We say an abstract graph is non-planar if there is no way to draw it in a plane without edges intersecting. Based on Kuratowski's Theorem, a graph is non-planar if and only if it contains K5 or K3,3. But this doesn't tell us anything about the conformation of the non-planarity in R^3. M-cluster in nitrogenase contains a Mobius ladder. The P-cluster in introgenase also contains a Mobius ladder with three rings. In conclusion, 5 questions are discussed as follows:
Can a knot occur in protein backbone through a process other than threading a terminus through a twisted hairpin? Does the knot 5_1 occur if we consider disulfide bonds as well as the protein backbone? Are there other protein structures that contain K_5 or K_3,3 but don't contain a Mobius ladder? Are there metalloproteins that contain a Mobius ladder with 5 rings? What role, if any, do knots, links and Mobius ladders in proteins play in enzymatic activity?

On Simplification of DNA Topology by Type II DNA Topoisomerases
Alexander Vologodskii (New York University)
Type II DNA topoisomerases can change DNA topology by catalyzing the passing of one double-stranded DNA segment through another. In 1997 Rybenkov et al. unexpectedly found that the enzymes can greatly reduce, up to hundred times, the fractions of knotted and linked circular DNA molecules comparing with the corresponding equilibrium values. The phenomenon of topology simplification attracted a lot of attention because it was very difficult to understand how small enzymes could determine topology of large DNA molecules. It seems clear now that the only way for the topoisomerases to achieve topology simplification is to use the fact that the probability of some specific local conformations of DNA segments depends on DNA topology. Although great progress has been made in understanding the phenomenon, some features of it are not explained by the existing models. To eliminate the discrepancy with the experimental data we suggest here a new model of the enzyme action.

Minimal molecular surface: PDE modeling and fast generation
Shan Zhao (Ohio State University)
When an apolar molecule, such as protein, DNA or RNA, is immersed in a polar solvent, the surface free energy minimization naturally leads to the minimal molecular surface (MMS) as the dielectric boundary between biomolecules and the surrounding aqueous environment. Based on the differential geometry, we have generalized the MMS model through the introduction of several potential driven geometric flow PDEs for the molecular surface formation and evolution. For such PDEs, an extra factor is usually added to stabilize the explicit time integration. Two alternating direction implicit (ADI) schemes have been developed based on the scaled form, which involves nonlinear cross derivative terms that have to be evaluated explicitly. This affects the stability and accuracy of these ADI schemes. To overcome these difficulties, we recently propose a new ADI algorithm based on the unscaled divergence form so that cross derivatives are not involved. This new ADI method is found to be unconditionally stable and more accurate than the existing methods. This enables the use of a large time increment in the steady state simulation so that the proposed ADI algorithm is very efficient for biomolecular surface generation. In

conclusion, this talk discussed molecular surface models - potential driven geometric flow PDES, and introduced numerical algorithms, which includes stable and fast ADI algorithms and adaptive time integration. Future work includes more tests on ultra large proteins and software development.

Measuring Molecules using Persistent Homology
Konstantin Mischaikow (Rutgers University)
Persistent homology is discussed in this talk, from classical algebra to Krull-Schmidt. A persistence diagram is a multiset consisting of one point for each persistence pair. Infinitely many points are included at each point on the diagonal. A Theorem is proved stating that a persistence diagram is a Lipschitz continuous function (Cohen-Steiner, Edelsbrunner, Harer).

The assumptions are: ignoring noise and ignoring tunnels and cavities that are too large. The ratio of H_2 persistence points to H_1 persistence points measures size of pockets. For dense granular media, experimental data has been obtained. Numerical simulation (Lou Kondic, NJIT) has been investigated. Finally, scalar fields (magnitudes of normal forces between particles) are obtained.

Packing, folding and simplifying DNA topology
Mariel Vazquez (University of California, Davis)
Cellular processes such as replication, recombination, and packing change the topology of DNA. Controlling these changes is key to ensuring stability inside the cell. We use topological and computational methods to study the action of enzymes that simplify the topology of DNA during replication. DR. Marquez reviewed these methods and expanded on some thoughts on DNA folding. 3D organization is the key to the proper functioning of the cell. However, high-resolution visualization is lacking. The Escherichia coli genome is segregated into independent topological domains of variable length and placement (average length 10kb). Chromosome territories. There is experimental evidence that each chromosome occupies its own territory during interphase. Evidence of topological domains in the human genome. What is the 3D conformation of DNA within one chromosome? Comprehensive mapping of long-range interactions reveals folding principles of the human genome. HI-C experimental protocol. The overall structure of the genome can be quantified by the contact probability graphs. Comparison between the equilibrium globule and the fractal globule proposed by Grosberg. The fractal globule (Non-equilibrium, space filling, largely unknotted, self-similar) is consistent with chromosome territories. The BFACF algorithm (Berg, Foerster et al) Dynamic MC method simulates self-avoiding walks. BFACF moves generate conformations without changing the knot type.

Complexity aspects of RNA folding on complex conformation spaces
Yann Ponty (Ecole Polytechnique, CNRS)
The prediction of the most stable, prevalent and/or functional structure adopted by an RNA molecule is an old, yet very much ongoing, challenge of computational biology. A gene big enough to specify and enzyme would be too big to replicate accurately without the aid of an enzyme of the very kind that it is trying to specify. RNA is single-stranded and folds on itself, establishing complex 3d structures that are essential to its functions. RNA

structures are stabilized by base-pairs, each mediated by hydrogen bonds. Currently available computational methods, such as MFold or RNAfold, tend to artificially restrict their search space to tree-like conformations. However, such a definition intrinsically discards complex topological motifs that are both observed in experimentally-determined structures, essential for the functions performed by the molecule, and conserved throughout the evolution. In this talk, Dr. Ponty reviewed two decades of works aiming at characterizing the complexity of minimizing the free energy of a given RNA molecule, while allowing (limited subsets of) pseudoknots/crossing interactions. The general hardness of the associated computational problems motivates the development of novel parameterized-complexity approaches and heuristics, as further illustrated by the follow up talk by H Orland.

Molecular Network Control Through Boolean Canalization
David Murrugarra (University of Kentucky)
Boolean networks are an important class of computational models for molecular interaction networks. Boolean canalization, a type of hierarchical clustering of the inputs of a Boolean function, has been extensively studied in the context of network modeling where each layer of canalization adds a degree of stability in the dynamics of the network. S. Kauffman introduced the concept of canalizing Boolean rules. The origins of order: Self-organization and selection in evolution. The term canalization was coined by the geneticist C.H. Waddington in the 1940's.

Recently, dynamic network control approaches have been used for the design of new therapeutic interventions and for other applications such as stem cell reprogramming. This talk will discuss the role of canalization in the control of Boolean molecular networks. A method for identifying the potential control edges in the wiring diagram of a network for avoiding undesirable state transitions will be presented. The method is based on identifying appropriate input-output combinations on undesirable transitions that can be modified using the edges in the wiring diagram of the network. Moreover, a method for estimating the number of changed transitions in the state space of the system as a result of an edge deletion in the wiring diagram will be presented. These two complementary methods can help in the selection of appropriate controllers such as for minimizing the side effects resulting from an edge manipulation. In summary, this talk exploits the canalizing properties of Boolean rules to derive a method that can be useful for identifying control targets for avoiding undesirable states.

THURSDAY, OCTOBER 1, 2015

Spatial rigid vertex graphs and RNA-guided DNA rearrangements
Natasa Jonoska (University of South Florida)
Gene structure is complicated. Dr. Jonoska and collaborators study homologous DNA recombination, in particular, rearrangements guided by RNA templates. The idea of Genes as beads on a DNA string is fast fading and RNA is a key part of the information package. In some cases, RNA may even pass information across generation.

Certain species of ciliates undergo massive DNA rearrangements during their development and are considered model organisms to study these processes. Dr. Jonoska showed that a four-valent rigid vertex graph can provide a physical representation of the DNA at the time of recombination. She associated operations on such graphs with template guided rearrangements and investigate their properties and showed that such an operation leads to the ``proper order'' of the DNA sequence after recombination. Schematically, the braiding process can be represented as a crossing (vertex) in such a graph. The homologous recombination corresponds to removal of the crossings in the graph (called smoothing). She then discussed properties of such graphs motivated by DNA assembly, genus ranges, and rearrangement pathways. In particular she analyzed these properties and rearrangement patterns for recently sequenced genome of ciliate Oxytricha that contains thousands of scrambled genes.

In summary, odd-even repeat and return patterns account for 81.7% of the scrambled genes – nested repeat/return account for 96.4% of the scrambled genes. Do similar patterns appear in other rearrangement processes? These patterns suggest that scrambling and genetic rearrangements are not random. (These patterns may adhere for a better selection process and may be conserved evolutionary.) There is still no evidence about the topological structure of the molecules during the rearrangement. (long template injections guide rearrangement, also about 800 MIC limited genes are discovered, some include topoisomerases and other bending enzymes).

Analyzing biological data via topological terrain metaphors
Yusu Wang (Ohio State University)
This talk introduces visual analysis and exploration of high-dimensional data. There is a critical need to map to low-dimensional space including such techniques as dimensionality reduction and Mapper methodology. In particular, Dr. Wang talked about the use of topological terrain metaphors for (biological) data visualization and analysis and then described two softwares she and her collaborators developed: Denali, a generic tool for visualizing tree-like structures (such as clustering trees) using topological terrain metaphors, as well as Ayla, a specialized visual analytic tool for exploring molecular simulation data. In conclusion, Dr. Wang introduced a visualization platform for High dimensional data based on scalar trees and terrain metaphors. In future, she will investigate stable terrain output, dynamic terrain/ time-varying, feedback loop to input sampling process.

Cooperativity of RNA Folding Landscapes
Sarah Woodson (Johns Hopkins University)
This talk discussed RNA fitness landscapes (Gene->3d->function) and cooperativity of RNA folding landscapes, including modular components of RNA structure. Active site at the interface between helical domains in a group I ribozyme. The entire RNA must fold to attain its biological function. When an active site is not stable in isolation, uniform function implies “uniform” fold. Energetic “cooperativity” reflects probability that both contacts form simultaneously. 3D contacts are linked to triple helix. Cooperativity emerges early in RNA folding and makes assembly more specific. Mutations broaden the folding population. Misfolding mutations are less deleterious in the cell than in the test tube.

Crowding gives mutant RNAs. Crowding stabilizes active RNA. Crowding does not increase fraction of mutation and compensates for destabilizing mutations. Cooperativity is essential for faithful assembly of large RNAs.

Electrodynamics in Chemical Reactions
Robert Eisenberg (Rush University Medical Center)
Chemistry and biology require charges and flow. Creating an enormous need and opportunity for mathematics. Mathematics replaces trial and error with computation for molecular biology, drug design, batteries/fuel cells (electricity, computers, fluid dynamics, optics, structural mechanics). Math is needed to describe devices of biology and technology. Chemical reactions are described and analyzed using conservation of mass and the law of mass action. The conservation of mass does not imply the conservation of electric current, as can easily be seen by in the reaction A ←→ B ←→ C where I_AB ≠ I_BC. The two reactions involve different rate constants, which are customarily independent, so the currents cannot be equal under more than one condition! Electric forces are much stronger than diffusion forces: one percent change in net charge produces a force large enough to lift the earth; one per cent change in mass has hardly any effect. Dr. Eisenberg argues that chemical models cannot transferable (with one set of parameters) if they do not satisfy conservation of current. He then argues that conservation of current must be exact in models of chemical reactions in all conditions, locations, and times because the 'current' defined in Maxwell's equations cannot be stored, at all. Dr. Eisenberg and his colleagues are trying to construct such models, following the lead of colleagues in semiconductor and computational electronics, who have done this for years.

NMR of small RNAs as benchmarks for testing all atom predictions of RNA structure
Douglas Turner (University of Rochester)
The study of RNA is important since about 95% of DNA is inscribed into RNA. Insight into the structure of small and large RNAs are provided by experiments that provide: (1) NMR spectra and (2) chemical reactivity of individual nucleotides. This information is incorporated into computer programs to predict the secondary and three-dimensional structure of an RNA. Though the 3D structure is difficult to predict, these insights can lead to potential compounds for therapeutically targeting RNA. NMR reveals a new 3D motif, providing proton chemical shifts, distances, and torsion angles. The idea is to use quantum mechanics to yield an estimate of torsion, chose the tetramer and run simulations to compare to experiments. Unfortunately, simulations do not agree well with NMR observations – creating a strong need for further development on the "quantum mechanical based" force fields.

RNA-Puzzles: a CASP-like collective blind experiment of the evaluation of automatic RNA three-dimensional structure prediction
Eric Westhof (Institute of Molecular and Cellular Biology)
RNA-Puzzles is a collective blind experiment for evaluation of de novo RNA structure prediction. The goals are to (1) assess the cutting edge of RNA structure prediction techniques, (2) compare existing methods and tools, and (3) evaluate their relative strengths, weaknesses, and limitations in terms of sequence length and structural complexity. This talk reports the results of a first, collective, blind experiment in RNA 3D

structure prediction. The results give potential users insight into the suitability of available methods for different applications and facilitate efforts in the RNA structure prediction community in ongoing efforts to improve prediction tools. The creation of an automated evaluation pipeline to facilitate the analysis of future RNA structure prediction exercises is also presented.

Improving nearest neighbor parameters for RNA folding free energy change
David Mathews (University of Rochester)
RNA structure is hierarchical and therefore the secondary structure, the set of the canonical base pairs, can be predicted independently of the 3D structure. In the past, these predictions were based on the lowest free energy structure using the nearest neighbor model. This model employs two assumptions. First, the stability of the motif (base pair or loop) depends only on the sequence of that motif and the sequence of the directly adjacent base pairs. Second, the total stability is the sum of the stabilities predicted for each motif. This talk overviews three different approaches to prove the nearest neighbor rules, based off of wet lab experiments. Then, a new procedure is discussed where all optical meeting data is collected and fit to a function that does not require the two stage assumption. It is found that the TMfits are improved, implying the nearest neighbor parameters can be improved by fitting to the original data.

Geometric combinatorics and computations molecular biology: Branching polytopes for RNA sequences
Christine Heitsch (Georgia Institute of Technology)
Techniques from geometric combinatorics, including polytopes and their normal fans, have been previously used for parametric analyses of simple models for RNA branching configurations. One known weakness of the current nearest-neighbor thermodynamic model (NNTM) is the energy function which governs the branching of an RNA secondary structure. For computational reasons, the entropic cost is modeled as an affine function with three parameters. A very natural question to ask is: How does the optimal secondary structure depend on the branching loop parameters?

This talk presents a new computational framework, and proof-of-principle results, which give the first complete parametric analysis of the branching polytopes for real RNA sequences. This insight was fully developed using methods from geometric combinatorics to give a parametric analysis of the optimal configurations, addressing the dependence of prediction results on the objective function parameters. The new computational framework makes possible the analysis of branching polytopes for real RNA sequences for the first time. However, it remains to be seen whether the observed patterns in these proof-of-principle results are resulting from the structure of the thermodynamic optimization and/or the coding of structural motifs in the base pairing of these RNA sequences. Resolving this dichotomy will reveal much about the interplay between mathematics and biology in the prediction of RNA secondary structures.

FRIDAY, OCTOBER 2, 2015

A multiscale and multiphysical model for molecular self-assembly

Guowei Wei (Michigan State University)
Differential geometry can be used to determine minimal energy in terms of surface area and surface tension. Many biological structures are organized in such a way as to minimize energy. The mean curvature can be determined via approximation of an elliptical equation. The nonpolar model involves a combination of area, volume, and solvent/solute interaction terms. The Laplace-Beltrami equation can be used to solve the surface function, which determines the entire system. Three examples show the advantage of the nonpolar model over previously published models in terms of minimizing energy. This model can be enhanced by considering the charge density as well, leading to the full solvation model. In this case, polar terms are added to the nonpolar model. Applications of this model include electrostatic binding, protein folding, molecular dynamics, and even rational drug design. This model can be used to determine mean curvature of a variety of structures, but also to predict protein binding sites. The next term added to the model concerns molecular mechanics.

Pseudoknots and knots in RNA
Henri Orland (Institute de Physique Theorique, CEA-Saclay)
Basic properties of RNA are that it is a middle-sized, single-stranded biopolymer. There are several forms of RNA, and up to 90% of it is non-coding, the so-called 'junk' RNA. The conjugate pairs, and the non-canonical pairings, give rise to RNA folding. The RNA folding problem is to determine the list of paired bases; knowledge of the secondary structure can help to predict 3D structure. Several motifs are common: helix, internal loop, hairpin-loop, bulge, and multiloop, for example. Additionally, there are secondary structures known as pseudoknots; these include the H-hairpin, the kissing hairpin, and the loop bulge. There are a small number of pseudoknots, and they occur in a small percentage of base pairings. Planar secondary structures do not contain pseudoknots, and can be represented in a number of ways. The full partition function of a planar graph can be reconstructed, but determination of pseudoknots is NP-complete. In calculating the partition function, pseudoknots should be penalized based on their topological complexity. They are categorized by their genus, which is used in the penalty term. For genus 1 it is possible to write recursion relations. A database, the Pseudobase, is a repository of pseudoknot genus and frequency. In general, pseudoknots with higher genus are more common the longer the sequence. A refined energy model, steric constraints, and the question of whether or not there are knots in RNA are all issue for future work.

Autumn Workshop 2: Multiple Faces of Biomolecular Electrostatics (October 12-16, 2015)

Organizers: Emil Alexov (Clemson University), Bo Li (University of California, San Diego), Ray Luo (University of California, Irvine), Guowei Wei (Michigan State University)

Report by: Kimberly Fessel, Jeffrey Gaither, Wenrui Hao

MONDAY, October 12, 2015

Multi-level theory for protein structure and dynamics
John Zhang (New York University Shanghai)

In this talk, Dr. Zhang talked about the development of novel computational methods for accurate and efficient study of accurate prediction of protein structure; protein folding; free energy in protein-drug and protein-protein bindings. He demonstrated that the combined use of quantum-based polarized protein-specific charge (PPC) for protein and polarized nucleic acid-specific charge (PNC) for DNA were employed in molecular dynamics simulation to study the interaction dynamics between INT-DBD and DNA. Their study shows that the protein-DNA structure is stabilized by polarization and the calculated protein-DNA binding free energy is in good agreement with the experimental data. He then concluded that a positive correlation between the measured binding energy difference in alanine mutation and the occupancy of the corresponding residue's hydrogen bond. This correlation relation directly relates the contribution of a specific residue to protein-DNA binding energy to the strength of the hydrogen bond formed between the specific residue and DNA.

Quantifying the influence of conformational uncertainty in biomolecular solvation
Nathan Baker (Pacific Northwest National Laboratory)

Dr. Baker uses uncertainty to explore biomolecules, which exhibit conformational fluctuations near equilibrium states. He presented a general method to quantify the uncertainty of target properties induced by conformational fluctuations. This method is based on a generalized polynomial chaos (gPC) expansion, and constructs a surrogate model of the target property with respect to varying conformational states. This method is also able to increase the sparsity of the gPC expansion by defining a set of conformational "active space" random variables. With the increased sparsity, the compressive sensing method is employed to accurately construct the surrogate model. The performance of the surrogate model is demonstrated by evaluating fluctuation-induced uncertainty in solvent-accessible surface area for the bovine trypsin inhibitor protein system. Then he applies this method to Poisson-Boltzmann equation by using multigrid method and adaptive finite element method. This new framework is claimed to be generalizable and can be used to investigate the uncertainty of a wide variety of target properties in biomolecular systems.

Watching water motions at biological interfaces
Dongping Zhong (The Ohio State University)

In this talk, Dr. Zhong investigated water-protein interactions. He began with the context that water is a universal lubricant in life and plays a critical role in biomolecular structure, dynamics and function. He then presented the systematic characterization of water motions around protein surfaces and protein-DNA interfaces in real time. Moreover, he demonstrated that hydration water has a series of correlations between the dynamics and protein properties. Furthermore, he gave some examples of mathematical modeling in their textbook to show the surface tension and sensing energy of water. Finally, he showed the different states of water changing, and summarized his talk: Hydration-water contributes more to relaxation than proliferation.

Electrostatic interactions in protein structure, folding, binding, and assembly
Huan-Xiang Zhou (Florida State University)
Dr. Zhou first introduced electrostatic interactions, which are very important in physics and biological functions. He then explained that amino acids with ionizable side chains have important properties to proteins. His aim is to present a unifying theme among the various effects of protein charges and electrostatic interactions. He introduced some basic ideas of electrostatic interactions in proteins through some simple models. These ideas are used to elucidate the roles of electrostatic interactions in protein structure and folding. Furthermore, he presented the Gaussian-Chain model with experimental evidence to demonstrate the electrostatic free energy of a protein. Finally, he summarized his talk as three parts: spatial distributions of charged residues; folding and binding stability and binding kinetics.

What data-driven models of biophysics tell us about protein electrostatics
Julie Mitchell (University of Wisconsin, Madison)
Dr. Mitchell began her talk with two seemingly opposing statements: 1) Electrostatics are essential; and 2) Electrostatics are irrelevant. The remainder of Dr. Mitchell's presentation was dedicated to supporting both of these viewpoints through the use of data-driven protein-binding models. Machine learning techniques, specifically support vector machines (SVM), can be used to classify data into groups by maximizing the distance between grouped data points and segregation boundaries. Dr. Mitchell utilizes SVM classification models to predict native-like interfaces, allosteric hotspots, and other protein-binding events. She detailed various statistical metrics that can be used as criteria for success, and she also described several electrostatic features operating as inputs to her models. While electrostatic forces, such as hydrogen bonding potentials, aromatic interactions, and salt bridge locations, appear to be important features in some systems, these same forces are not statistically significant in others. It is known that electrostatics are critical in these processes; however, Dr. Mitchell argues that sometimes the environment surrounding the electrostatically meaningful site is even more imperative for predicting binding hotspots and characteristics such as deformability, packing, and reorganization capacity benefit the area more effectively.

Probing electrostatics and conformational motions in enzyme catalysis
Sharon Hammes-Schiffer (University of Illinois)
Both electrostatics and conformational motions play important roles during catalytic and ligand-binding events. Dr. Sharon Hammes-Schiffer studies these effects in two prototypic enzymes: dihydrofolate reductase (DHFR) and ketosteroid isomerase (KSI). Using a hybrid quantum-classical approach, Dr. Hammes-Schiffer simulates motion studies as well as electrostatic interactions computationally and determines characteristics such as stability, bond changes, and kinetic fluctuations for various protein residues. Thiocyanate probes can be used in experimental settings to elucidate electrostatic variations; Dr. Hammes-Schiffer explained how she employs 'computational probes' to illuminate changes during catalysis and protein binding. Through this work, she can attribute electrostatic shifts to particular the kinetics of specific residues. Dr. Hammes-Schiffer concluded by stating that stochastic thermal motions can lead to equilibrium

conformational changes, thereby facilitating chemical reactions, and electrostatic shifts along a catalytic reaction pathway are influenced by conformational motions.

TUESDAY, October 13, 2015

Beyond pairwise approximation for electrostatics

Teresa Head-Gordon (University of California, Berkeley)

Dr. Head-Gordon spoke about the development of a model for polarization that makes use of smart approximations for tractability, but does not lose favorable performance when calculating electron-electron interactions. While a tension between accuracy and sampling exists for this type of problem, Dr. Head-Gordon believes that with the use of proper estimations she has developed a solver for polarization that accomplishes an appropriate balance between cost and veracity. Approximating the interplay between N molecular bodies with 3-body interactions is crucial in Dr. Head-Gordon's model. She explained that other AMOEBA (Atomic Multipole Optimized Energetics for Biomolecular Applications) models yield good accuracy but are very expensive to implement. Dr. Head-Gordon has developed an improved AMOEBA solver, which retains predictability but is much less costly. After demonstrating a few example processes with her model, she ended by reiterating that the 3-body interaction is a well-defined approximation for mutual polarization and holds valid for both atomistic and coarse-grained electron problems.

Ionic atmosphere around DNA: role of ion correlation and solvation

Maria Sushko (Pacific Northwest National Laboratory)

Dr. Sushko aims to build simple models from first principles to describe experimental data without including any fitting parameters. She began by providing a description of classical density functional theory (cDFT) and highlighting its benefits and deficiencies. Most significantly, cDFT deteriorates for larger systems of electrolytes. Dr. Sushko has established a minimal model for bulk electrolyte solutions, which includes a term for direct short-range interactions, a significant improvement over cDFT. The ionic atmosphere around DNA can be studied with her model by representing DNA as either as a cylinder, akin to a mean-field approach, or a grooved tube. Dr. Sushko presented the results of her efforts and validated her findings with experimental outcomes. Ultimately, she concluded that ion-ion correlation interactions induce counterion penetration into the DNA grooves, while solvation delivers the opposite effect.

A new type of Poisson-Boltzmann equation modeling, computation, and biological application

Duan Chen (University of North Carolina, Charlotte)

Electrostatics serves as a critical influence in drug design, ion channels, and a plethora of other protein functions. Poisson-Boltzmann (PB) Theory remains a popular method for modeling electrostatic events; however, this mean-field approach lacks several key aspects including ion-ion interactions, variations for differing ionic species, and inhomogeneities in water such as its dielectric response. Dr. Chen seeks to improve the Poisson-Boltzmann model by including linearized, ion-specific dielectric functions. He has thus derived a new version of the PB equation using this simple modification, which

he has dubbed the quasi-linear Poisson-Boltzmann equation (QPBE). Dr. Chen uses numerics to solve this new formulation and ultimately adopts a finite difference scheme with a fixed-point Newton's method to arrive at his solution. He also discussed some direct applications of his work in which proteins are considered with the regular Poisson-Boltzmann equation but the surrounding solvent is treated with his improved QPBE. In the future he'd like to extend his work to consider entire ion channels.

Electrostatics beyond Poisson-Boltzmann: effects of self-energy
Zhen-Gang Wang (California Institute of Technology)

Salt ions affect structural phase behaviors in a variety of ways including impacts on charge neutrality, screening, and translational energy. Poisson-Boltzmann and Debye-Hückel are two common frameworks for describing electrostatic interactions; however, both theories exhibit inadequacies, which are prominent in polymer reactions as well as in the inhibition of bubble coalescence in high-salt concentrations. Dr. Wang attributes many of these inadequacies to the occlusion of self-energy, and his work focuses on detailing self-energy in a theoretical manner to predict and to understand the consequences of this important concept. His new theory involves an inhomogeneous, nonperturbative approach for investigating self-energy, and Dr. Wang spent the remainder of his talk developing a system of coupled equations and discussing qualitative phenomena that can be understood via his model. He stressed that it is critical to include the self-energy of ions when examining any dielectric change, which could manifest, say, as a phase transition or at the formation of an interface.

Beyond Poisson-Boltzmann approach in macromolecules electrostatics
Xueyu Song (Iowa State University)

Dr. Song wishes to improve upon the classic Poisson-Boltzmann description by straightforwardly examining the Maxwell equations in dielectric media. The dispersion relation from this analysis, which links spatial and temporal effects, can be associated directly with Poisson-Boltzmann (PB) theory. Using a boundary element method to solve the PB equation, Dr. Song computes the electrical potential as a combination of Debye modes. This approach can be used to study the electron transfer case in ionic fluids and tends to perform much better than classical Debye-Hückel theory for complicated fluids. Dr. Song presented several more applications of his work including comparisons to authentic experimental results. In general, he has found that the traditional PB approach can be improved by performing multiple linear PB calculations.

A treecode-accelerated boundary integral (TABI) Poisson-Boltzmann solver: features and applications
Weihua Geng (Southern Methodist University)

Dr. Geng introduced his talk by providing an overview of TABI and highlighting that it is a well-posed boundary integral formulation in which the equations have been discretized. He proceeded to illustrate TABI's tunable accuracy and favorable parallelization. Dr. Geng provided several comparison tables to show how TABI stacks up against other computational methods, and he discussed several benefits and disadvantages to each approach. His algorithm can be used for many real-world

calculations, and Dr. Geng then demonstrated how to measure pKa, polarizable multipoles, electrostatic forces, and molecular dynamics with TABI. He played a molecular simulation movie that had been compiled using TABI and ended by commenting that he would like to compute more force formulations with this technique in the future.

WEDNESDAY, October 14, 2015

A Treecode-Accelerated Boundary Integral Poisson-Boltzmann Solver for Electrostatics of Solvated Proteins
Robert Krasny (Rush University Medical Center)
Dr. Krasny first mentioned that this work is joint work with Weihua Geng (Southern Methodist University). He gave some background on electrostatic effects, which are very important in determining protein structure and function. He then presented a treecode-accelerated boundary integral (TABI) solver for the electrostatic potential of a solvated protein described by the linear Poisson-Boltzmann equation. The method employs a well-conditioned boundary integral formulation for the electrostatic potential and its normal derivative on the molecular surface. The linear system is solved by GMRES and the matrix-vector product is carried out by a tree code which reduces the computational cost. He also showed some comparisons of TABI results to those obtained using the finite-difference APBS code.

Partial Molar Volume Corrected Solvation Energies, Entropies and Free Energies from 3D-RISM
Tyler Luchko (California State University, Northridge)
Dr. Luchko talked about the water map and inhomogeneous theory. To begin, he presented his new method which is able to get the entropy solution. He then introduced the spatial decomposition by using initial correction but the results have no difference. There is also no difference for 3d simulations between his method and the traditional methods. He concluded that UC(T) and ISC corrections perform well for SFE; corrections also greatly improve solvation energy and entropy; corrections are a symptomatic remedy and can be applied to other solvent thermodynamics. In the future, they will add the effect of oxygen. The factor XA is connecting different regions and surface areas.

Why Multivalent Ions Condense DNA but Not RNA?
Alexey Onufriev (Virginia Tech)
Dr. Onufriev introduced his team members and collaborators, and gave an outline of his talk. Then he asked a question: How do multivariate ions condense nucleic acid? He gave a brief review of the importance of nucleic acids condensation: packing of genomes; packing for drug delivery. He then talked about the RNA catastrophe, and pointed out their connection with condensation propensities multiple ion binding shell (quantitative) model of nucleic acid condensation. Finally he summarized aggregation free energy and related components.

Electrostatics inside the SecY translocon protein that guides membrane protein assembly

Stephen White (University of California, Irvine)

Dr. White first introduced SecY, which constitutes the core of the highly conserved SecYEG translocon complex, and he also mentioned the important role in determining transmembrane topology via the so-called positive-inside rule. Then he presented molecular dynamics simulations of SecYE from Pyrococcus furiosus embedded in a POPC bilayer. Based on this simulation, he concluded that SecY in the P. furiosus structure is in a partially open 'primed' state and also that it conveniently remained open allowing close examination of the electrostatics within the translocon. Moreover, he introduced some applications such as water dipoles exhibiting a preferred orientation. Later he presented the time-averaged ES maps, which reveal a largely positive potential relative to the bulk aqueous phase within the channel except for a strong negative peak at the N-terminus of TM2b.

Role of Water and Ions in Enzyme Catalysis: from Mechanistic Insights to Modulator Design

Yingkai Zhang (New York University)

Dr. Zhang first presented an interesting calcium dependence in a biological system that needs two calcium to function, but only one calcium is identified in the crystal structure. Then he presented that a prerequisite is to reliably compute free energy barriers for chemical reactions in enzymes and solutions. Is this due to the mechanism difference? In order to answer this question, he presented a model to explain the transition state of the solution reaction. He talked about their computational approaches based on Born-Oppenheimer ab initio QM/MM molecular dynamics simulation (aiQM/MM-MD) with umbrella sampling. It undergoes a significant change from the pre-action state to the transition state. Based on the computation, he discovered a novel time-dependent HDAC2-selective inhibitor. In addition, hel briefly described AlphaSpace – fragment centric topographical mapping to target protein-protein interaction (PPI) interfaces. Finally, he concluded that targetable pocket space can be used to guide the rational design.

Modeling of enhanced catalysis in multienzyme nanostructures: effect of molecular scaffolds, spatial organization, and concentration

Chia-en (Angelina) Chang (University of California, Riverside)

Dr. Chang began by introducing association processes and overall enzyme catalysis, biological spatial organization, bioengineered spatial organization, model systems. After giving some details on modeling of enzyme nanostructures, she then summarized the math models in three groups - analytical solution, simplified monte carlo, and brownian dynamics. After that, she introduced the GeomBD program which includes spatial scaffolding and system concentrations. Some computational details are explained in both simple 2d models and more detailed models. In her simulations, intermediate transfers between two planes. She also evaluated the impact on reaction probability and impact on efficacy with different system concentrations. The conclusion is that the math model and simulation results highlight the importance of protein geometry in the proper assessment of distance and orientation dependence on the probability of substrate transfer.

THURSDAY, October 15, 2015

Differential Geometry based Multiscale solvation models and their computation
Zhan Chen (Michigan State University)

Solvation is the process by which molecules are dissolved in a solvent. As a great many different chemical reactions, both synthetic and natural, occur in a solution state, the details and precise description of the process of solvation represents a manifestly important problem. In this talk, Dr. Chen outlined his work on the theory of solution mechanics, upon which he brought to bear techniques from differential geometry. The key component of his methodology is a free energy functional, whose value varies as it roams about the system and whose effects can be focused on different scales. One triumph of this new approach is that it contrives a reduction in the number of parameters. It also handles more smoothly than other paradigms in the tricky region where solvent and solute actually interact.

What can quantum-inspired electrostatics methods contribute to biomolecular applications?
John Herbert (The Ohio State University)

Dr. Herbert's research focuses on quantum-mechanical electrostatics in general and is specifically interested in the interface of this field with biology, described two ways in which the study of quantum electrostatics can yield insights on biological problems. He presented his work on refined dielectric continuum solvation models (which are called "PCMs" in the parlance of the field), which to some degree resolves a longstanding roadblock in electrostatics-contribution computations. These methods boil down to solving Poisson's equation, but require that only the cavity-surface (which is two-dimensional) be discretized rather than the whole space, which results in a large gain in efficiency. He also presented an algorithm for applying perturbation theory to systems containing many bodies, which has applications to the interaction of a ligand with the amino acid residues of its bound-to protein.

Improving Short-range Electrostatic Model for Molecular Interaction
Pengyu Ren (The University of Texas at Austin)

Dr. Ren presented a new model for the short-range electrostatic penetration effect that occurs between molecular clusters. The specific goal of the model was to take advantage of the large data-gathering capacities of SAPT ("symmetry adapted perturbation theory," which is a suite of computer programs) to gain a more thorough understanding of the effect in question. Traditionally, the researcher models short-range electrostatic penetrative effects in this context via the method of atomic point monopoles; however, Dr. Ren's new model demonstrably improves upon the old technique. The electrostatic effects upon which the talk focuses represent a substantial component in the modeling and calculation of bio-molecular binding in general, and this new paradigm therefore advances and hones, in a not-enormous but nevertheless identifiable and non-negligible way, the state of the art in bio-molecular interaction theory.

Structural/energetic analysis of protein-based interactions: highlighting the electrostatics contribution
Irina Moreira (Center for Neuroscience and Cell Biology)

Dr. Moreira presented some work which considered the electrostatistical factors in protein-based interactions, especially with regard to structure and energy. In the setting of biomolecular physics "structure" and "energy" are highly correlated, since the likelihood of a structure increases as its free energy decreases. The contribution of electrostatics is obvious for DNA and RNA, since both are positively charged; but in the case of protein-protein interactions, where a strong charge is not a necessary condition, the role of electrostatics is more subtle. Protein-protein interactions tend to be quantified by the free energy of the resultant structure, and specifying the contribution of electrostatics force to this is an important goal. However, there are the difficulties that the binding takes place in an aqueous environment which is constantly changing (in ways relevant to the electrostatic perspective), and also that the electrostatic energy of the protein-players themselves will typically change during the binding process. Dr. Moreira outlined some means of coping with these difficulties and generally attacking the problem of electrostatics in this context.

BION webserver: electrostatics based prediction of surface bound ions
Marharyta Petukh (Clemson University)

An important and difficult problem in computational molecular biology is the locating of ions that are bound to the surfaces of macro-biomolecules. Dr. Petukh presented a new algorithm, known as BION, which can predict the positions of ions on the surface of proteins using the geometrical and electrostatic interactions between the two. The procedure employs a sophisticated clustering technique in conjunction with pairing rules, which in the end yield a very satisfactory level of accuracy. The tool BION is actually available online. Dr. Petukh demonstrated the utility of BION by applying it to Chronic Beryllium Disease, as well as TAR/TSR bacterial chemoreceptors.

Electrostatic interactions play important roles in kinesin proceeding on microtubule
Lin Li (Clemson University)

A kinesin is a mobile protein which is responsible (among other tasks) for the transportation of of biological cargo along microtubules. Though this is a fundamental biological interaction in eukaryotes, its precise underpinnings remain surprisingly cloudy. In this talk Dr. Li related some recent work investigating the influence of electrostatic effects on the locomotion of kinesins. As one of the principal difficulties in modeling the kinesin-system is a near-prohibitively large number of components, Dr.Li's approach was to model the system stochastically rather than deterministically, electing to apply a Monte Carlo approach in simulations. The simulation revealed potential valleys dug around the microtubule, which forced the kinesin to traverse it longitudinally rather than latitudinally.

FRIDAY, October 16, 2015

Dipolar materials
Ridgway Scott (University of Chicago)

Dr. Scott gave a short introduction to the phenomenon of dipolar materials and their relevance to biomolecular electrostatics. The idea of a dipole is particularly relevant to biology since the classic example, namely water, is a compound central to all known life. As one focal point to his talk, Dr. Scott presented the Madelung constant, which quantifies how energetically a collection of dipoles interacts with itself on a macro scale. Substances whose dipoles globally coordinate (and therefore have high Madelung constants) are said to be ferromagnetic. He then discussed some of the mathematical aspects of modeling dipoles, and in particular how to interpret divergent sums.

Biomolecular electrostatics beyond Poisson-Boltzmann
Patrice Koehl (University of California, Davis)

The classic paradigm for understanding the electrostatic properties of macromolecules is the Poisson-Boltzmann equation, which is a partial differential equation that basically aims to describe the effect of electrostatic forces on molecules in solution. In this talk Dr. Koehl introduced a new viewpoint whereby, in contrast to Poisson-Boltzmann, one regards the surrounding medium not as homogenous dielectric soup but rather as a discrete assemblage of numerous self-orienting dipoles. This is a considerable modification to the classic model, and one qualitative effect of the addition is that the dielectric constant in the solvent region takes on aspects of a variable. Dr.Koehl conceded that this model does have limitations, but emphasized that new solutions are being developed despite the increased complexity, which will extend the model's field of relevance.

Free Energy Driven Geometrical Simulation of Protein Dynamics
Donald Jacobs (University of North Carolina, Charlotte)

Proteins appear to be ubiquitous in life, and a given protein has a lot of different properties that collectively determine how it interacts with itself and with other molecules and media. Furthermore, when considering the behavior of proteins it is important to take into account intrinsic properties of the underlying medium, such as its temperature. All these different facets, together with the usual difficulty of predicting the behavior of a large system of particles, make large-scale protein dynamics a difficult phenomenon to simulate. In this talk Dr.Jacobs summarized two common approaches to this problem: DSMs (Distance Constraint Models) and GS (geometric simulation. He then presented a new model which is a hybrid of these two types, and which is driven by a careful consideration of the free energy of the system in question. The basic idea is to solve for a free energy functional in each iteration, thereby pushing the system forward. There is the usual balance to strike between accuracy and speed.

Autumn Current Topic Workshop 1 - Uncertainty, Sensitivity, and Predictability in Ecology: Mathematical Challenges and Ecological Applications (October 26-30, 2015)

Organizers: Jennifer Dunne (Santa Fe Institute), Alan Hastings (University of California, Davis), Andrew Morozov (University of Leicester)

Report by: Jeffrey Gaither, Karly Jacobsen, and Ying Zhou

MONDAY, OCTOBER 26, 2015

Predictability, uncertainty and the persistence of ecological populations
Alan Hastings (University of California, Davis)
The speaker began with an overview of different types of stochasticity and uncertainty, including stochasticity (e.g. Jensen's inequality), model uncertainty (e.g. Lotka-Volterra), data measurement error, "tipping points" (bifurcations). The speaker then presented a very interesting work that links a model to experiments about the spatiotemporal dynamics of flour beetle (*Tribolium castaneum*). In the analysis of the experiment data, it was found that the best fitting model was the one that included all the heterogeneity and stochasticity factors. The work presented considered both non-spatial and spatial models, and looked at both questions in invasion speed and range distributions under climate change. The take-home message is that large noise may be the important case for ecology.

Evaluating structural sensitivity of partially specified models in ecology
Andrew Mozorov (University of Leicester)
The speaker began with explaining the idea of "structural sensitivity", which is the phenomenon when two different models fitting the same dataset yields substantially different model predictions. This is a challenging problem to tackle, and the speaker presented a framework that uses partially specified models (ODE models where unknown functions are represented not by a specific functional form, but by an entire data range). This framework is useful in detecting structural sensitivity in models, and the approach is to project the data range into a generalised bifurcation space formed of equilibrium values and derivatives of any unspecified functions. There is a mathematical challenge here on how to carry out this projection, and the challenge is addressed by geometrical methods and techniques from optimal control theory. Finally, the speaker introduced the idea of "functional density", which is a degree of sensitivity, which allows us to estimate uncertainty in partially specified models.

Structural sensitivity in food web models
Gregor Fussmann (McGill University)
The speaker discussed structural uncertainty in the choice of ecological functional response, arguing that dynamical predictions are sensitive to the choice. This was first exemplified in a comparison of Holling type 2, Ivlev and trigonometric functional responses in a two species predator-prey system. Bifurcation structures were further compared in more complex trophic architectures including enrichment and multiple prey species. While the stabilizing effect of exponential and trigonometric functions vs. Holling type 2 appears to vanish in food webs, other differences remain. In particular, the Ivlev response showed larger amplitudes of oscillation in predator population, and the minima was better bounded away from zero. With two prey, the Ivlev and TanH responses also demonstrated persistence over a larger range of carrying capacities.

The second part of the talk focused on sensitivity to source of prey defense (i.e. genetic and constitutive vs. plastic and inducible) and trophic location of defense (autotrophic prey vs. heterotrophic prey). Results indicated that plasticity generally promotes stability more than genetic diversity while both sources promoted persistence equally. In addition, variation at the herbivore level was shown to promote stability and persistence more than variation at the autotroph level. Finally, various prey-density dependent functional responses were considered including sigmoid, saturating, and unimodal forms. Prey-density dependent components (PDCs) were shown to promote stable coexistence of predator-prey systems more often than not. Strong stability was demonstrated for 69% of the datasets considered, suggesting that PDCs are probably common in nature and predictions of instability based on Holling type 2 are likely overstated.

TUESDAY, OCTOBER 27, 2015

Including individual properties in community and ecosystem models: is it useful and how should we proceed?
Jean-Christophe Poggiale (Institut Pytheas (OSU), Aix-Marseille University)
The speaker began by discussing some problems observed with ecosystem models using examples from the literature. The speaker then introduced an approach to build models on a mechanistic basis by relating individual properties to population and community level dynamics, and used the functional response in predator-prey systems as an example. One challenge in building models is that data may only be available from experimental settings, but researchers may want to build models for natural environments. The speaker introduced scaling-up methods to tackle this challenge. Scaling up methods provide explicit links between different organization levels or between several temporal/spatial scales. The speaker then presented several examples in marine system modeling.

Generalized models of food web dynamics
Thilo Gross (University of Bristol)
In this talk, the speaker introduced an approach of generalized modeling, which describes the dynamics of a complex 'networked' system without restricting the dynamics in the network nodes to specific functional forms. This approach is very efficient and can be used to answer many ecological questions. The speaker and his colleagues were thus able to analyze a large set of network structures and reveal important insights about foodweb stability. Examples of the application of this method include the impact of climate change on mammal communities in Egypt, identification of key species in an aquatic system, and general results about foodweb stability.

Long range synchronization of oscillating populations without external forcing described by Ising universality
Jon Machta (University of Massachusetts)
In this talk, the speaker introduced some relevant concepts from statistical physics. These concepts and tools are helpful in understanding the onset and maintenance of long-range order in thermodynamic systems and these tools can be applied to spatially explicit population models relevant to ecology. The speaker showed how to apply these tools to locally-coupled, noisy ecological population models, and showed that short range

dispersal may initiate and sustain global synchrony over distances much larger than the dispersal length scale, even in the presence of strong local noise and inhomogeneities.

The effect of sparse and noisy data in ecological monitoring and pest control
Natalia Petrovskaya (University of Birmingham)
In this talk, the speaker discussed how to quantify the effect of data sparseness and noise in the pest insect monitoring problem. Many ecological problems require monitoring and sampling of alien populations, where the information obtained as a result of monitoring is then used for making decision about means of control. In ecological applications, data used for decision making are often sparse due to financial, labor, and other restrictions on the sampling routine. The same sparse data can also be noisy because of the inherent nature of the ecological problem. One example of a monitoring procedure based on sparse and noisy data is given by a widespread and important problem of pest insect abundance evaluation from the insect density in an agricultural field. An inaccurate estimate of the pest abundance obtained because of uncertainty in data can result in the wrong decision about a control action (e.g. unnecessary application of pesticides). The speaker showed that noise is a negligible factor in comparison with the uncertainty of evaluation arising as a result of poor sampling.

WEDNESDAY, OCTOBER 28, 2015

Nonlinearity and chaos in ecological dynamics: revisited
Ottar Bjornstad (Pennsylvania State University)
The speaker first gave a brief history of the quest for exactitude in ecology. He explained there had long been the hope of ecological phenomena being described in terms of simple equations, with noncentral external factors playing only a peripheral role. In the 1970s and 1980s, certain equations gave the ecological community reason to hope that such paradigms might indeed be realized. However, in more recent days the field of ecology at large has grown mistrustful of the idea of all-governing equations and embraced the importance of unpredictability and chaos. The speaker then outlined a few case studies that illustrate the importance of essentially unpredictable inputs. For example, "low dimensional dynamics," a way of looking at an ecosystem that consists of many species using comparatively few parameters, was observed to be unreliable in capturing the effects of decisive irregularities. Again, models that predicted measles outbreaks were presented as often inadequate because they did not allow for irregularities in (for example) birth rates following a war.

Understanding the perverse implications of conservation actions: modelling ecosystems with limited information and guiding system-wide conservation monitoring and management
Eve McDonald-Madden (University of Queensland)
The speaker discussed some of the pitfalls that can arise when one sets out to help a species without taking its ecosystem into account. One example was that of the introduction of wolves into Yellowstone Park, which (perhaps unsurprisingly) led to the predation of those wolves upon large mammals already living in the park (among them elk), which in turn brought about deleterious effects on the park's vegetation and water

flows. In some cases, the hoped-for "conservation" can actually deplete the population of the species one is trying to protect. Furthermore, the effects of actions designed to substantially affect a single species' fortunes, even for the better, are extremely difficult to predict because of the interconnected nature of and potential for feedback in ecosystems. Another case study elucidated by the speaker is that of the plan to exterminate feral cats from Christmas Island. The logic behind this plan is that the cats are bringing about the extinction of many species native to Christmas Island; however it is not entirely clear that the elimination of the cats would improve the situation in the long run.

Why structural instability is inherent to ecological communities and how management can deal with it

Axel Rossberg (University of London)

Structural instability is the tendency of a system to undergo fundamental qualitative transformations as a result of small changes in parameters or external pressures. In the case of ecological systems, instabilities often arise via extirpations (or local extinctions). The speaker argued, using both models and data, that structural instability increases with species variation, and that at a certain point even one additional species can (on average) be expected to lead to the extirpation of another. As an example he presented fisheries, and briefly discussed the problem of breeding a variety of fish in the same environment in a manner that is robust against catastrophe. He divided the options of a manager faced with the problem of structural instability into two categories: either manage one's stock at a higher level, or contrive and maintain artificial ecosystem states in which the desired equilibrium can be preserved.

Approaches and Uncertainties in Predicting Coastal Ecosystem Changes Due to Rising Sea Level

Donald De Angelis (University of Miami)

The speaker talked about the effects of rising sea levels on plants, particularly in southern Florida. Sea levels are rising worldwide, which is bad news for organisms that live near coasts but in a freshwater environment. The rise of sea levels is in particular eliminating vegetation which depends on a ready supply of freshwater (such vegetation is said to be "glycophytic") and clearing up spaces for flora which can tolerate a certain amount of salt in its water. However, predicting the extent to which salt-resistant plants will displace freshwater-dependent plants is uncertain. External factors such as hurricanes are most difficult to incorporate with any regularity, and in addition the feedback interactions between the organisms in the ecosystem complicate the mathematics substantially. Nevertheless this is an important problem and the speaker presented some models that give us reason to hope that important progress might yet lie ahead.

The irreducible uncertainty of the demography-environment interaction in ecology

Per Lundberg (Lund University)

A pervasive problem in ecology is that of separating demography (true information about births and deaths of organisms) or other properties of the ecosystem, from environment (noise and random fluctuations that say nothing about true trends). This problem is not

unique to ecology, but ecology is inexact enough, and sensitive enough to external changes, that the problem is particularly worrisome here. The author explored the problem of noise in biology – what it means, and whether trying to cope with is worth it or even possible – with a few examples and some philosophy. As an example, abiotic factors can as a rule be disregarded as "noise" more safely in a terrestrial than in a marine environment.

THURSDAY, OCTOBER 29, 2015

A survey of the mathematical theory of early-warning signs: scaling laws near criticality

Christian Kuehn (Vienna University of Technology)

Dr. Kuehn's work on detection of early-warning signs for drastic transitions is motivated by various critical transitions in ecology such as extinction, desertification and ecosystem control. He began the talk with an overview of the theory behind multiple time scale dynamical systems, covering both deterministic and stochastic fast-slow systems. The remainder of his talk focused on the singular case where the critical manifold is not normally hyperbolic. The main idea presented was that, in stochastic fast-slow systems with small additive white noise, the variances increases as the system approaches a bifurcation point; thus, noise from the time series can be used as an early-warning system. Therefore, methods for transition detection focused on the attracting critical manifold and included consideration of the variational equation for the linearized process. A classification theorem was presented which gave generic scaling laws for covariance up to codimension two. Employing a moment expansion method, explicit results for leading-order covariance scaling were also given. Two biological applications were provided: the Bazykin predator-prey system, and a pyramidal neuron *in vitro*. The speaker concluded by discussing challenges in the theory of early-warning signs such as extensions to more complicated models and dealing with noisy and spatial factors simultaneously.

Animal movement in dynamic landscapes: Quantifying patterns and modeling processes

Bill Fagan (University of Maryland)

Dr. Fagan began by emphasizing the need for ecological models to incorporate dynamic landscapes with time- and space-varying attributes such as availability or quality of resources, size or location of habitats, and connectivity among habitats. He first talked about persistence of populations in patches that change size over time using the framework of an integro-difference equation model with a novel habitat suitability function. Analysis of this system showed that population persistence hinges upon the magnitude of variation in habitat size. Dr. Fagan continued with a discussion of empirical work on migratory variation and its correlation with resource availability as measured by the normalized difference vegetation index (NDVI). Absolute mean annual NDVI was found to be the strongest predictor of migration distances, with a negative correlation coefficient. The next strongest predictor was the range of NDVI, with a

positive correlation coefficient. The third part of the talk focused on nomadic animals; in particular, movement and population redistribution patterns of the Mongolian gazelle were characterized. A very strong autocorrelated signal in gazelle movement data motivated the development of new statistical tools. As opposed to the correlated random walk model, the framework developed was time lag analysis, comparable to "variogram analysis" in econometrics or geostatistics. Movement is modeled as a continuous stochastic process that is observed at discrete times where different movement models can be specified via the semi-variance function (e.g. random search, anomalous random search, random search plus utilization range and the latter plus foraging). Subsequent fitting to the movement variogram allows for model selection. Results of the corresponding analysis for the Mongolian gazelle were presented, indicating again that individual gazelle ranges correlate with scale of resources experienced.

Evolutionary dimensions of ecological uncertainty and predictability
Robert Holt (University of Florida)
The talk opened with a discussion of broad challenges in developing a general theory of ecology-evolution-environment and understanding how trait-mediated interactions affect the resolution of classic ecological problems. The remainder of the talk focused on shorter time scales where evolutionary dynamics can be ignored, in particular the study of niche conservatism. Evolutionary rescue in the presence of discrete changes in the environment was explored, first in a heuristic model of geometric growth with time-varying fitness. The speaker demonstrated that evolutionary rescue depends on heritability of the trait under selection, initial population size and magnitude of environmental change. Predation was then introduced into the model and food web interactions were also shown to affect the likelihood of evolutionary rescue for demographic reasons (by affecting rate of decline) and for genetic reasons (due to correlation among traits). An individual-based model which incorporated demographic stochasticity and genetic drift was also presented. Results indicated that probability of adaptation (i.e. evolutionary rescue) goes to zero with increasing sink maladaptation and increases with initial population size. An experimental demonstration of evolutionary rescue was also given; yeast populations exposed to high salt concentrations can demonstrate this behavior. Dr. Holt concluded by emphasizing that evolutionary rescue depends on the trajectory of environmental change (i.e. abrupt vs. sequential changes) and conjectured that persistence reflects a continual input of variation.

Nonparametric approaches to ecological dynamics and ecosystem management
Steve Munch (University of California, Santa Cruz)
The speaker presented a nonparametric Bayesian framework as a method to deal with structural uncertainty in models for population management applications. Unknown components of partially specified dynamic models, such as forms of functional responses, were inferred based on Bayesian updating of zero mean Gaussian process (GP) priors. A host-parasitoid system served as an example where semiparametric inference was performed on the functional response of surviving host fraction. Dr. Munch extended the framework to ecosystem-based management that required a more general approach due to the multitude of missing components. Takens theorem was employed in order to perform Bayesian time delay embedding. Hierarchical models were presented allowing for the

simultaneous consideration of a combination of time series datasets, each with their own GP prior drawn from a hyperprior distribution. Results were presented as one-step forecasts resulting from fitting to synthetic training sets simulated from a range of models including multi-patch spatial models. The scenario of a changing environment was studied using nonstationary GPs that dramatically influenced the precision for one- and two-step forecasts. The speaker concluded by discussing the particular application of the methodology to fishery management. Combined with dynamic programming, the GP dynamic models produced harvest policies with good performance that was close to ideal constant effort policy and better than performance of the standard Ricker model.

FRIDAY, OCTOBER 30, 2015

Giving "noise" the respect it deserves: ways to understand and visualize effects of stochasticity in ecological dynamics
Karen Abbott (Case Western Reserve University)
The stochastic component in a population dynamics problem is often viewed as "noise" which obscures the big picture. However, the speaker made the case that, more frequently than is commonly considered, stochastic effects play a fundamental role in determining the intrinsic properties of a system. This is a relatively new idea – not only because it is conceptually somewhat counter-intuitive, but also because it is mathematically difficult to implement, stochastic effects being harder to model than deterministic effects. As one example, the midges of Lake Myavin have two stable population-states, in which food is either very scarce or very abundant, and the transition from one state to the other is an entirely stochastic phenomenon. As a converse to the thesis that noise is important, the speaker posited that in many cases we should rethink and loosen our notion of "stability" so that it can capture equilibria that sometimes exist even in perturbation-sensitive systems.

Uncertainties in Modeling Patchy Invasion: Effect of Long-Distance Dispersal
Sergei Petrovskii (University of Leicester)
The speaker discussed two paradigms for the invasion of a new species, emphasizing new interest in the "patchy invasion" model over the classic "continuous front" model. The orthodox way to model an invasion of, say, insects is as a continuous line which divides the area into two connected pieces, one invaded and one not. But the comparatively new patchy invasion model assigns different densities of invaders to different regions, so that a given patch may be heavily populated by intruders, and yet a region between two patches may be less densely invaded (or entirely untouched). The central point of the speaker's talk was that patchy invasions can occur even when the effects of long-distance dispersal are incorporated into the model. The mathematical formulation of this thesis is via integral-difference equations with fat-tailed dispersal kernels. One of the speaker's findings was that species spread seems rather sensitive to perturbations in the parameters, which goes along the workshop's theme of uncertainty in ecology.

Top down, bottom up or pragmatism?

Odo Diekmann (Utrecht University)
Dr. Diekmann concluded the workshop with a broad discussion of modeling approaches as well as some recent results on renewal equations. Citing the work of Don Ludwig, he emphasized the need for pragmatism in model development due to noise in data and the need for robustness. He further discussed top down and bottom up approaches. An example of the top down approach was shown via the work of mathematician Weinberger impacting field experiments by phytopathologists on the mixture of yield and vulnerability traits. The bottom up approach was exemplified by the recent outbreak of Ebola where theoretical questions arose based on the specific need for a public health response. However, the speaker emphasized that bottom up and top down are different methods of getting started, but ultimately the goal is a full connection and influence in both directions on the line between mathematicians and public health. The speaker also talked about renewal equations, recalling the derivation of Kermack and McKendrick and incluced a recent result giving a necessary and sufficient condition for a renewal equation to be equivalent to an ODE with full information. A renewal equation for the case of an epidemic spreading on a configuration model graph was also discussed, based on the work of Miller and Volz. He concluded with a discussion of the advantages of the renewal equation framework and an overview of recent work that aims to provide a set of tools for the methodology.

Autumn Workshop 3: Modeling and Computation of Transmembrane Transport (November 16-20, 2015)

Organizers: Benoit Roux (University of Chicago), Guowei Wei (Michigan State University), Marie-Therese Wolfram (Austrian Acadamy of Sciences, RICAM)

Report by: Richard Buckalew, Casper Woroszylo, Wenrui Hao

MONDAY, November 16, 2015

Regulation of conductance in K channels
Simon Bernèche (University of Chicago)
The third workshop was concerned with studying the fundamental question of how ions go through channels. The motivating example introduced potassium channels, which are trans-membrane proteins that have the ability to conduct K^+ ions. High-resolution crystallography as well as computer models, namely molecular dynamic (MD) simulations, have facilitated an interest in refinement and understanding of these systems. The two-dimensional potential mean force (PMF) associated with the various positions along of pore of the proteins were calculated using umbrella sampling of the potassium channel from *Streptomyces lividans* (KcsA). MD simulations and various modifications throughout the years reproduced formerly known binding sites and anticipated the existence of additional sites, which were independently verified from data.

General steric trapping strategy reveals an intricate cooperativity network in the intramembrane protease GlpG under native conditions
Heedeok Hong (Michigan State University)

Dr. Hong discussed developing methods for studying membrane protein foldings under native conditions using a technique called steric trapping. In particular, key areas of interest in studying these proteins are thermodynamic stability, compactness of the unfolded state, and unfolding cooperativity under native conditions. Steric trapping is a two-state method composed of linking the binding of monovalent streptavidin (mSA) to the unfolding of biotinylated protein (MP). This allows for measurements of high affinity protein-protein interactions and thermodynamic stability of polytopic helical MPs in a native environment. Target specific approaches in steric trapping have been a limiting factor is studying various MP systems.

Dr. Hong et. al. developed biotin probes possessing spectroscopic reporters that are sensitized by mSA binding or protein unfolding. Applying these methods to an intramembrane protease GlpG yielded a widely unraveled unfolded state, local unfolding of the region containing the active site, and a network of cooperative and localized interactions for maintaining the stability. Hence, steric trapping can aid in studying local versus global flexibility of helical MPs.

Modeling Proton Transport in Transmembrane Proteins with Multistate Reactive Molecular Dynamics
Heather Mayes (University of Chicago)
Dr. Mayes models the Influenza A M2 protein channel, the ClC antiporter, and the SERCA channel. Such systems are multiscale (from micro- to femto-second and from protein to proton) and thus difficult to simulate. The primary mechanism of ion transport through these channels is the Grotthuss mechanism.

The first part of this presentation was a history of MS-RMD methodology (Multistate Reactive Molecular Dynamics), as the technique grew from valence bond models to superposition of electron states, through Hamiltonian approaches and optimization techniques on the Helmann-Feynman operator. MS-RMD techniques are faster than Quantum Mechanics / Molecular Mechanics methods by ~3 orders of magnitude.

She then showed applications of MS-RMD to the aforementioned channels. Using the technique she discriminated between “shuttle” and “shutter” type mechanisms in the Influenza A M2 channel by investigating multiscale models of the protonation state of various proteins within the channel. The model also elucidates the role of water-wire paths within SERCA and ClC channels, and the positional dependence of ClC on a single Cl- ion.

Particle Counting Method to Enforce Concentrations in Dynamic Simulations
Claudio Berti (Rush University Medical Center)
Dr. Berti’s talk centered on ways to implement boundary conditions for ion concentrations in ion channel simulations. This is a difficult problem due to the discrete nature of molecular level models. Dr. Berti introduced an efficient method, called PACO (Partical Counting), and compared its accuracy and efficiency with GCMC (Grand Canonical Monte Carlo) methods.

The PACO method shrinks boundary cells and introduces new regions beyond the boundaries on either end, then integrates the population in the control cells over time and compares with the desired boundary condition. Only when this difference is at least one in magnitude, the method then inserts a new ion to maintain the desired concentration.

Due to re-entry of molecules into the control cell, the naive method causes an uneven concentration profile within the control cell so that at the boundary, it is still too low compared with the desired boundary condition. Dr. Berti solved this problem by tracking individual ions and only deleting those that originated in the other control cell - on the other side of the simulated ion channel.

PACO stabilizes in approximately 10,000 steps and increases the speed of simulation steps by ~2 orders of magnitude. There is an optimal control cell width for "flatness" and time average concentration accuracy.

Energetic Variational Approaches in General Diffusion for Charged Particles
Chun Liu (Penn State University)
Dr. Liu discussed energetic variational approaches as a method to study the movement of charged particles. The energetic variational framework for classical mechanics was originally introduced in work by Rayleigh and Onsager. For isothermal situations, a dissipative system satisfies the Second Law of Thermodynamics, namely that the total energy changes with respect to the dissipation functional, which happens to be entropy production. The Least Action Principle states that the equation of motion in a Hamiltonian system can be derived from the variation of the action functional with respect to the flow maps. This provides a unique way of deriving conservation forces for the system. The Maximum Dissipation Principle, i.e. dissipation functional with respect to the rate (e.g. velocity), gives the dissipative force for the system.

These approaches were used to explore stationary configurations of the Ernest-Planck-Poisson equations and limiting behavior as the Debye constant becomes small. They also yield well-posed solutions in convection-diffusion equations of Fokker-Planck type systems. These diffusive interactive methods have led to developed system and numerical algorithms to model deformation of vesicle membranes with preferred ion selection.

Progress in understanding C-type inactivation
Benoit Roux (University of Chicago)
C-type inactivation is a conformational change at the selectivity filter, the ion binding site in a K^+ channel that renders it non-conductive. This type of inactivation is important in controlling cellular excitability. In 2000, Dr. Roux et al. developed a computational algorithm based on Grand Canonical Monte Carlo (GCMC) and Brownian Dynamics (BD) that was used to simulate the movement of ions in membrane channels. The proposed method allows the simulation of these ion channels with a realistic implementation of boundary conditions of concentrations and transmembrane potential with an example in OmpF porin of E. coli. In 2013, Dr. Roux et. al. extended the simulation techniques to allow realistic ionic gradients and asymmetric salt

concentrations while maintaining conventional periodic boundary conditions that are needed to minimize finite-size effects in an all-atom explicit solvent representation.

Work on macroscopic behavior of KcsA in pH jump experiments has shown that inactivation and deactivation gating of KscA are predominantly modulated by pH without a significant effect of voltage. The NaK channel is a cation selective channel with similar permeability for K^+ and Na^+. Potential of mean force for complete conduction events of the two ions through the channel show that large energy barriers prevent the passage of ions through the wild type channel structure. A long lived inactivated state is controlled by binding of 12 water molecules to the selectivity filter. Recovery from inactivation requires the release of inactivating waters and rebinding K^+ ion, showing the importance of water in entry into an inactivation state.

Tuesday, November 17, 2015

Voltage-gated sodium channels

Ke Dong (Michigan State University)

Voltage-gated sodium channels are integral transmembrane proteins that are important in electrical signaling for most excitable cells. Because of their critical roles in electrical signaling, sodium channels are effective targets of a variety of naturally occurring and synthetic neurotoxins including pyrethroid insecticides. These neurotoxins bind to distinct receptor sites and alter sodium channel functionality by blocking the pore or altering channel gating. Dr. Dong discussed that different sodium channel isoforms yield distinct gating properties. Molecular and functional diversity was evaluated using RNA splicing. Mammalian sodium channels are more resistant to pyrethroids than insects. Pyrethoid-sensitive mammalian sodium channel were developed since high-affinity pyrethoid binding sites are lacking in mammals. Structural features that are critical for mammalian Na channel function are conserved in insect sodium channels.

Investigating the Selectivity of KcsA Channel by an Image Charge Solvation Method (ICSM) in Molecular Dynamics Simulations

Wei Cai (University of North Carolina, Charlotte)

Dr. Cai presented work studying the selectivity of the potassium channel KcsA by using the image-charge solvation method (ICSM) combined with molecular dynamics simulations. ICSM is a hybrid electrostatic approach that combines the strengths of both explicit and implicit representations of the solvent. A multiple-image method is used to calculate reaction fields due to the implicit solvent while the Fast Multipole Method (FMM) is used to calculate the Coulomb interactions for all charges, including the charges in the explicit solvent part. The hybrid solvation model in the ICSM is able to demonstrate the function of the selectivity filter of the KcsA channel at the atom level when potassium and sodium ions are considered and their distributions inside the filter are simulated. In particular, the model shows that the reaction field effect, explicitly accounted for through image charge approximation in the ICSM model, is necessary in reproducing the correct selectivity property of the potassium channels.

Membrane proteins: from structure refinement and remodeling to functional mechanisms

Huan-Xiang Zhou (Florida State University)

Ion channels and other membrane proteins, relative to water-soluble proteins, have less intrinsic stability and are more prone to influences of the solubilizing environments. To achieve native-like structures, Dr. Zhou used solid-state NMR data for refinement through restrained molecular dynamics simulations in native-like environments, i.e., in lipid bilayers. For the influenza M2 proton channel, the focus of study was on its functional center, where a histidine tetrad within the channel pore acts as both the pH sensor and ion selectivity filter. Structure determination via solid-state NMR and refinement via MD led to developing a mechanism for acid activation and proton conductance.

Dr. Zhou developed a theoretical model using this mechanism and was able to quantitatively rationalize the M2-mediated currents solvent isotope effect and dependences on pH and transmembrane voltage. In glutamate receptors, structure refinement and remodeling was performed on two subtypes, namely AMPA, NMDA. Similar work was done to study the helix interactions within the transmembrane domain of P2X receptors. This leads to general approaches to studying the conformational space of channel pores, namely pore-lining helix (PLH) bundles.

MD modeling of ion and substrate transport through porins

Ulrich Kleinekathöfer (Jacobs University Bremen)

Channels in the outer membrane of Gram-negative bacteria provide essential pathways for the controlled and unidirectional transport of ions, nutrients and metabolites into the cell. At the same time the outer membrane serves as a physical barrier for the penetration of noxious substances such as antibiotics into the bacteria. Dr. Kleinekathöfer studied the simulation of ion and substrate transport across such bacterial channels using MD simulations in the transport of ions. Electrophysiology forms a promising approach to study the permeation of molecules across outer membrane and thereby understanding molecular interactions with the channel. However effects due to external applied voltage on the molecular permeation in porins remain unclear in this technique. Voltage effects are even prominent on neutral molecules which are related to the presence of electro osmosis flow.

Dr. Kleinekathöfer presented a biophysical characterization of CymA from *K.oxytoca* which has the ability to take up cyclodextrin (neutral molecules). Detailed single channel analysis revealed inherent asymmetric gating characteristics of the channel. There was also voltage dependent interaction of neutral molecule (cyclodextrin) with CymA presumed due to Electroosmosis. To further explain these effects, substrate interaction studies were performed under various external conditions. To obtain an atomistic view, we complement our studies BD simulations were used to study the flow of water and also its directionality in the channel in the absence and presence of substrate. Dr. Kleinekathöfer has explicitly shown the existence of such an effect in the outer membrane uptake channel.

The Molecular Dynamics of Potassium Channel Gating, Permeation, and Selectivity
Bert de Groot (Max-Planck-Institut)
Dr. de Groot's talk was organized into four parts: pH gating of aquaporin-4, computational electrophysiology, K+ permeation, and gating in K2P channels.

Histadine 95 flips transiently in simulations and crystallography studies of the aquaporin-4 channel. Protonating His95 increases channel permeability by 25%, and the effect is confirmed by Functional Mode Analysis. His95 knockout channels do not show sensitivity to pH. The mechanism appears to be an increase in energy well density along the length of the channel, making ion transport by brownian motion more likely.

Internal voltage is simulated by extending the model to periodic boundary conditions, and adding a second channel, of the form 0=0=0. By applying a potential to the center compartment, a voltage drop across the channel is simulated.

Simulations indicate that K+ permeation through KcsA open state structures occur only when water molecules leave the filter, indicating that ion-ion contact is the primary driver of K+ permeation. This mechanism appears to be similar to that in many other ion channels.

Simulations of K2P channels illuminate the quick gating mechanism and the mutation behavior in T103C and T212C knockouts, which depends on the number and location of binding sites in the filter.

Molecular Mechanisms of Selective and Efficient Ion Translocation Across Biological Membranes
Ulrich Zachariae (University of Dundee)
Dr. Zachariae's talk made for an appropriate continuation of the previous one, further explaining the simulation methods introduced there. The main focus of his talk was exploring the seeming contradiction of strong affinity (thus selectivity) combined with high transport rate in a channel.

Simulations of PorB porins elucidate the mechanism of wild-type channels, having both anionic and cationic pathways, vs. that of mutants which lack the cation path.

For K+ selectivity, simulations reveal that Na+ abd K+ binding sites are different within the pore, and Na+ is blocked at the S4 binding site. The result is that when an Na+ ion is present in the channel, "knock-on" cannot happen between the K+ ions and this prevents current.

Wednesday, November 18, 2015

Interrelationships Between Cellular Ca2+ handling and Intercellular Communication
Perumal Nithiarasu (Swansea University)

Dr. Nithiarasu's goal is to use Ca2+ dynamics to predict disease. His overall goal is a modeling platform for understanding endothelial dysfunction, and to provide for non-invasive testing of drugs targeting cardiovascular disease, as an *in silico* pharmacological model. His current goal is predicting the concentration of eNOS species via single cell models, but he finds that clinical data is scarce. Thus he has turned to smooth muscle cells.

Dr. Nithiarasu uses electrical activity as a proxy for drug efficacy in smooth muscle cells. He first gave an overview of the Excitation-Contraction Coupling pathway. Then he showed an experimental setup composed of fluorescing cultured cells and gold calibration disk-measured vasomotion, to measure pressure and flow. He then presented an ODE model due to Parthimus et al and verified the results of the model by simulating verapamil, ryanodine, ionomycin and carbenoxolone.

His next project is to build a model of a "virtual artery", incorporating single cell Ca2+ models into large scale simulations.

Dual Phase Field Modeling of Endocytosis
Yongcheng Zhou (Colorado State University)
Dr. Zhou is interested in mechanisms of diffusion across the plasma membrane for polar molecules, for which the membrane is generally impermeable. Such mechanisms are called endocytosis, consisting of active transport as the molecule is engulfed by the cell. Dr. Zhou coats nanoparticles with ligands to induce endocytosis, and models the binding energies of the membrane, which depend on particle size and ligand choices. In particular, he is interested in disguising particles as cancer cells to study the dynamics of cancer.

Dr. Zhou uses a phase field model for the process, whereby a function is nonpositive outside the cell and positive on the interior. The function is used to define the curvature energy of the membrane. A similar, nondeformable function is defined for the nanoparticle and the interaction between them can be described using the sum of the two functions.

The results include: moderately sized particles diffuse more quickly than either large or small ones; higher charges diffuse faster than lower ones. By including diffusion of receptors on the membrane surface, Dr. Zhou is also able to describe and drive diffusion to target regions of the cell.

A Numerical Method for Electrokinetic Flow with Deformable Interfaces
Michael Booty (New Jersey Institute of Technology)
Dr. Booty presented a vastly complex partial differential equations model for the dynamics at the interface between two regions, representing a vesicle, or the surface of a drop of solvent. He then described asymptotic analysis of the model for thin Debye layers, resulting in data describing the relationship of field strength and deformation size, as well as steady state and time-dependent solutions of the model.

Ion Transport in a Channel: 3D Finite Element Modeling Approach and its Applications

Benzhuo Lu (Chinese Academy of Sciences)

Dr. Lu uses finite element analysis to model ion channels. He starts with a continuum model (PNP), adds point charges for protein atoms, and generates a mesh based on this data. The mesh is constructed very carefully to ensure separation of molecule volumes, using Gaussian Surface methods to guarantee a "manifold" mesh. The Gaussian surface is parameterized, and its quality is comparable to other methods. Numerical systems are then solved on the mesh (such as PNP, SMPNP, SUPG).

One application of the method is to simulate insertion of DNA into a channel. Dr. Lu then demonstrated a comprehensive tool for visualization of models and simulations, and cloud-based tool his team has implemented to provide for such visualization from existing data sets.

On Cross Diffusion Systems for Particle Transport in Confined Geometries

Marie-Therese Wolfram (RICAM)

Dr. Wolfram is interested in the transition region between microscopic and macroscopic models, called mesoscopic. She builds mesoscopic models by starting with a microscopic model, discretizing to a lattice, and describing discrete dynamics on the lattice. She then takes the scaling limit as the grid step size goes to zero, resulting in a PDE model which she can then analyze.

Cross-diffusion is the phenomenon of two diffusing particles influencing one another, including particles of quite different sizes. Dr. Wolfram studies such phenomena using entropy methods, which allow her to translate the system into a "gradient flow" form. In an SDE variation of the model, entropy no longer provides a Lyapunov-type decreasing functional; rather the entropy is linearly increasing. When particles are different sizes, even linear growth cannot be achieved. Thus she finds the entropy only up to order O(epsilon^2), which provides an approximate gradient flow, which can then be used to find approximate solutions to the system.

Modeling and Simulation Approaches for Ion Permeation and Gating in Protein Ion Channels

Maria Kurnikova (Carnegie-Mellon University)

Dr. Kurnikova discussed various modeling and simulation approaches to ion permeation and gating in protein ion channels. In Brownian dynamics (BD), ions are modeled explicitly, but water is treated implicitly as a continuous medium characterized by dielectric and friction constants. In Poisson-Nernst-Planck type sytems, ions are represented by continuous densities. The most common approach used is molecular dynamics (MD). The entire system, including water, is modeled explicitly, and the dynamics of all atoms is computed. Hence, the method is the most accurate, but very slow (compared to BD and PNP). The total PMF can be approximately split into long range interaction and short range repulsion. To model alpha-hemolysin (AHL), a general version of PNP, the potential mean force PNP (PMFPNP) was used in a soft repulsion

(SR) model of short range interactions between permeating ions and protein atoms lining channel lumen. Using PNP-SR, an optimized membrane position, and a relaxed channel yielded results similar to experiment. This method was used in modeling divalent ion selectivity in main excitatory receptors in the brain. In particular, NMDA receptors were modeled in glutamate ligand-gated voltage-dependent ion channels.

Thursday, November 19, 2015

Fermi Poisson Description of Ions in and out of Channels
Robert Eisenberg (Rush University Medical Center)
Dr. Eisenberg first introduced valves control on flow, which are nanovalves channels. He followed that with some classical theory and simulations for thermodynamics and statistical mechanics. He then talked about mathematical issues of devices, which are fascinating and nontrivial. It means that everything involves non-ideal ionic mixtures, divalents. Then he asked a question to the audience "where to start? ". Hiological adaptation and crowded charge is a good starting point. Dr. Eisenberg then used some examples to explain that active sites of proteins are very charged. Fermi's description of saturation of volume has exact consistency with complex electrodynamics of flow. A Fermi-like distribution is a general quantitative statement of charge-space competition. Finally he gave some evidence to show the application of Fermi-like distributions in chemistry with correct mathematics.

Ion flow properties from analysis of Poisson-Nernst-Planck type systems
Weishi Liu (University of Kansas)
Dr. Liu first gave some background on Poisson-Nernst-Planck (PNP) equation and ion channel structure. He then presented a model that he works on: A quasi-one-dim PNP model for ionic flows. He gave some results of geometric singular perturbation for this PNP model. By introducing boundary conditions, he reformulated the Boundary Value Problem (BVP) to a concentrating problem. Then he pointed that the matching gives the governing system for singular orbits of the BVP. The analysis allows us to track the nonlinear interplays between relevant physical quantities and to extract critical information on ionic flow properties, such as effects of ion sizes, permanent charges and channel geometry. Also a number of concrete consequence for ionic flow are mentioned to apply in the future.

Modified PNP_steric equations: a new model of ion transport through channels
Tai-Chia Lin (National Taiwan University)
Dr. Lin first talked about the importance of ion channels for our whole body. Ion transport through biological channels is very crowded. He then asked the question "How do we describe ion transport?" He then presented his PNP type model for crowded ions by including steric effects from ion sizes. The original PNP model is without steric effects. Then he briefly mentioned the numerical scheme of the modified PNP_steric equations, which is developed to see the flow dynamics of charged particles. By using gating and selectivity, their numerical results show that the energy of the modified PNP_steric equations may behave like a decreasing piecewise constant function of time.

Finally he used some example to demonstrate of the usefulness of the study for ion transport through channels.

Modeling and Simulation of Ion Flow in Biological Channels Including Electrochemical, Fluid, Thermal and Mechanical Forces
Riccardo Sacco (Politecnico di Milano)
In this talk, Dr. Sacco proposed a multiphysics model for the simulation of biological ion channels by using a continuum-based approach. This approach combines ion electrodiffusion, channel fluid motion, thermal self-heating and mechanical deformation. The formulation of this mathematical model includes a system of nonlinearly coupled partial differential equations in conservation form, and includes the thermo-velocity-extended Poisson-Nernst-Planck equations, the Stokes equations, the Navier-Lame' equations and the heat equation. The validation of this model has been done by comparing the simulation of two realistic channel geometries under quite different operation regimes. By considering a cylindrical voltage operated ion nanochannel transport and the interplay between the motion of ions, they validate this new developed model. The results show very good agreement with available experimental data and biophysical conjectures.

Models of multicomponent lipid bilayers: curvature and endocytosis
Keith Promislow (Michigan State University)
Dr. Promislow began with some background on lipid bilayers, which are composed of a multitude of lipid constituents. The distribution over the inner and outer leaflets of the plasma membrane are known to have predetermining influence on membrane curvature and endocytotic events. In this talk, he presented a minimal continuum model of lipid membranes that supports families of bilayer morphologies. He then investigated the stability and slows geometric evolution of multicomponent bilayer interfaces within the context of gradient flows of the mFCH, addressing the impact of aspect ratio of the lipid/copolymer unit on the intrinsic curvature and the codimensional bifurcation. He also derived a Canham-Helfrich sharp interface energy whose intrinsic curvature arises through a Melnikov parameter associated to lipid aspect ratio. Finally he showed that the dominant co-dimensional bifurcation mechanism is via the layer-by-layer pearling observed experimentally.

"The importance of being superficial": how efficient surface representation can aid in bio-molecular simulation
Walter Rocchia (Istituto Italiano di Tecnologia)
Dr. Rocchia began with an introduction to the Solvent Excluded Surface (SES), which is a concept that dates back to the 1970s. SES is mainly used in defining the separation between high and low dielectric constant regions in Poisson-Boltzmann (PB) calculations. Then Dr. Rocchia talked about its construction, which is fundamental in the Boundary Element Method solution of the linearized PB equation. However, the notion of SES and the availability of an efficient tool to compute it can be extremely useful also in other contexts and with volumetric approaches to PB equation solution. He then illustrated the main features of the NanoShaper tool and gave two examples where they are exploited. The solution approach for the Finite-Differences PB makes use of accurate

surface information mitigating the need for higher resolution and allowing the treatment of larger systems. The Molecular Dynamics protocol for estimating water persistency in given regions of a simulated system exploits the notion of the SES to distinguish buried water molecules from those that more easily can access the bulk.

Friday, November 20, 2015

Nonlinear models for nanopores
Jan-Frederik Pietschmann (University of Münster)
Dr. Pietschmann began with rectifying nanopores which feature ions, which are higher for voltages of one polarity compared to the currents recorded for corresponding voltages of the opposite polarity. He then mentioned that the experimental observations could not be explained by a continuum modeling based on the current Poisson–Nernst–Planck equations. So he introduced a class of non-linear variants of the well-known Poisson-Nernst-Planck Model and discussed its properties as well as possible applications to ion channels and nanopores. He also presented a formal derivation based on a one-dimensional lattice model, and argued that the model is more well-suited for high densities in confined geometries.

Modeling electrostatics in biological membranes and membrane proteins: Applications to human diseases
Emil Alexov (Clemson University)
Dr. Alexov first gave some background on the 3D structures of membrane proteins, which are typically determined without the presence of a lipid bilayer. Then he mentioned that for the purpose of studying the role of membranes on the wild type characteristics of the corresponding protein, determining the position and orientation of transmembrane proteins within a membrane environment is highly desirable.

He next presented a geometry-based approach to automatically insert a membrane protein with a known 3D structure into pregenerated lipid bilayer membranes with various dimensions and lipid compositions or into a pseudomembrane. The method developed is implemented into a web server, the ProBLM server, which is freely available to the biophysical community. The user is given an option to manually refine the model by manipulating the position and orientation of the protein with respect to the membrane.

Variational multiscale modeling of ion channels
Guowei Wei (Michigan State University)
Dr. Wei gave a survey of differential geometry-based multiscale and multiphysics paradigms for ion channel systems. He then described their approaches by using macromolecular systems. These approaches include macroscopic electrostatics and elasticity and/or microscopic molecular mechanics (MM) and quantum mechanics; while treating the aqueous environment as a dielectric continuum or electrolytic fluids. In order to solve the system, differential geometry theory of surfaces is used to couple various microscopic and macroscopic domains on an equal footing. Based on the variational principle, he derived the coupled Poisson-Boltzmann, Poisson-Nernst-Planck (PNP), Kohn-Sham, Laplace-Beltrami, and Newton equations for the structure, function,

dynamics and transport of ion-channel systems. Finally he mentioned some homology modeling to construct mosquito sodium channels and combination of MM and PNP type of approaches for the understanding of sodium channel gating.

Autumn Workshop 4 - Mathematical Challenges in Drug and Protein Design (December 7-11, 2015)

Organizers: Eric Cances (Ecole des Ponts), Michael Gilson (University of California, San Diego), Martha Head (GlaxoKlineSmith Pharmaceuticals), Ridgway Scott (University of Chicago).

Report by: Matthew Oremland, Farrah Sadre-Marandi, Casper Woroszylo

MONDAY, December 7, 2015

Oncogenic K-Ras: The Undruggable Protein
Ruth Nussinov (National Cancer Institute)
Dr. Nussinov presented the history and motivation for studying KRAS proteins. There is a high incidence of RAS mutations in cancer, with no drug targets or therapies developed. KRAS alleles in particular have a distinct biology and we don't understand why. Mechanistic questions of interest were: (i) Do RAS disordered hypervariable regions (HVR) have a role beyond membrane anchoring; (ii) Does RAS dimerize?; (iii) What pathways and mutations are relevant?; (iv) What's the role of Calmodulin? Dr. Nussinov discussed these questions in the context of an isoform of KRAS, called KRAS-4B. HVRs have a role in prevention of premature signaling, auto-inhibition, and shift the ensemble to an active state. She found that KRAS-4B dimerizes using PRISM and predicted 4 dimer interfaces. Oncogenic mutations suggest that they play a role in more than abolishing gtp hydrolysis. Calmodulin binds to KRAS-4B but not HRAS or NRAS.

Challenges in system-level drug design
Valeriu Damian (GlaxoSmithKline)
Many drug candidates fail due to lack of efficacy which may be for the following reasons: (i) Does the drug reach its targets? (ii) If the drug reaches its target, does it engage its target? (iii) If the drug reaches its target and engages it, is there a desired response? The main issue is that design has been driven by the one drug-one target-one disease model when in fact, there are usually multiple targets within interacting biological processes within heterogeneous diseases. The main idea is to develop more mechanistic approaches, namely physiologically-based pharmacokinetics (PBPK) and quantitative and systems pharmacology (QSP), discussed in an NIH white paper by Sorger et. al. The idea is to develop models that predict the right target with differentiation using a rock solid foundation. Dr. Damian produced examples in lysosomal storage diseases and acne.

Sampling challenges in protein-ligand binding free energy calculations
David Mobley (University of California, Irvine)
Modest improvements in the accuracy of sampling in protein-ligand free energy calculations can have significant benefits. In 2013, Dr. Mobley et. al. published work on

free energy calculations in structure-based drug design. Using a progression of model binding sites allows for free energy method development. The idea is to generate starting conformations using docking with separate calculations for different orientations. Some protein conformational changes present sampling problems and bias results. Over-polarization of the force field could lead to charge-charge interactions that are too strong. Hence a new tool is proposed that calculates relative free energy. Dr. Mobley concluded that in order to sample more efficiently, one must consider multiple orientations of the molecule of interest, which can make nontrivial predictions. Conformational change of a protein is key in performing free energy calculations. Large scale relative calculations are practical. Protein modeling in general remains a major challenge, especially in sampling.

Variational Implicit Solvation with Application to Identifying Ligand-Protein Binding Sites

Bo Li (University of California, San Diego)

Dr. Li discussed variational implicit solvation methods (VISM) used in understanding ligand-protein binding sites. Issues in biomolecular models are hydrophobic cavities, curvature corrections, and decoupling polar, nonpolar, and dispersive connections. One approach, introduced in 2006 by Dzubiella is VISM. The idea is to formulate a free energy functional composed of volumetric energy, surface energy, solute-solute interactions, and electrostatic energy. Dr. Li outlined how to incorporate dielectric boundary forces, a level set method approach, fluctuations and atomistic motions, and applications to identify binding sites. He showed that level set VISM can capture multiple hydration states and charges effects. The method provides good estimates, is efficient, and can be applied to protein-ligand binding and protein-protein interactions. Issues that remain are charge asymmetry, dielectric boundaries, solvent entropy, and the hydration shell.

TUESDAY, December 8, 2015

Adaptive Multilevel Splitting algorithms for rare event simulations

Tony Lelievre (École des ponts ParisTech)

Under stochastic dynamics, namely Langevin equations, Dr. Lelievre and his group studied sample paths between two metastable states. The issue is that metastable states have energetic and entropic barriers, providing slow convergence of trajectory averages. Using level sets and the strong Markov property, Dr. Lelievre showed that one can construct the trajectories in such a way that is computationally tractable using stopping time arguments and probability arguments. Various estimators and associated statistical properties have been proved with respect to the sample paths and time to reach the metastable state. This method, called the adaptive multilevel splitting (AMS) algorithm has been implemented in the NAMD software.

Grand Canonical Solute Sampling in Combination with the Site Identification by Ligand Competitive Saturation (SILCS) Ligand Design Methodology

Alex MacKerell (University of Maryland)

Site identification by ligand competitive saturation (SILCS) presents a concept known as FragMaps. This involves MD sampling of the phase space by a small molecule in aqueous

solution, resulting in a two-dimensional probability distribution. Defining the protein surface based on solute / water exclusion maps allows for a better sampling scheme. Furthermore, probability distributions are converted to grid free energies (GFE). The proposed method involves Ligand GFE (LGFE) combined with monte-carlo (MC) sampling. SILCS is limited by solute sampling in occluded pockets, rate of diffusion of organic solutes, and time scales of protein conformational changes. Dr. MacKerell introduced grand canonical ensemble based on MC sampling (GCMC) wiith alternating MD simulations with an example in water. The idea is to mix MD simulations with GCMC until convergence. This allows for accessing systems with deep or totally occluded binding sites.

Orthogonal Space Sampling of Slow Environment Responses
Wei Yang (Florida State University)
Dr. Yang discussed free energy sampling by following perturbations along order parameters to sample important events in the orthogonal space. This can involve geometric perturbations (PMF calculations) or chemical perturbations (FEP calculations). Sampling slow environment responses involves appropriately defining an order parameter, namely a generalized force, to explore the orthogonal space. Lambda-dynamics allows the unification of PMF and FEP sampling. This leads to high-order orthogonal space tempering (HOOST), in which weakly coupled environment responses are defined as a response to lambda-dynamic force fluctuations. This allows for accurate prediction of protein functional dynamics.

pH-dependent BACE1 activity and inhibition
Jana Shen (University of Maryland at Baltimore)
BACE1, a major therapeutic target for treatment of Alzheimer's disease, functions within a narrow pH range. Despite tremendous effort and progress in the development of BACE1 inhibitors, details of the underlying pH-dependent regulatory mechanism remain unclear. Modeling efforts include discrete Monte Carlo simulations and continuous equations. Recent work in exploring the pH-dependent conformational mechanism that regulates BACE1 activity and substrate/inhibitor binding using continuous constant-pH molecular dynamics is presented. Advantages and drawbacks of various methods are compared, most notably in terms of convergence. Free energy surfaces can reveal multiple conformational states. Current drug developers Merck and Lilly currently have inhibitors with similar binding interactions but with variations in binding affinity. The new insights greatly extend the knowledge of BACE1 and have implications for further optimization of inhibitors and understanding potential side effects of targeting BACE1.

Binding hot spots, druggability, and ligand deconstruction
Sandor Vajda (Boston University)
Binding energy hot spots, smaller regions of binding sites that contribute a disproportionate amount to the free energy of binding any ligand, can be determined computationally from ligand-free structures of protein targets. The consensus site of probe binding has been shown to be critical. The hot spot structure of a protein target provides very useful information on binding properties. The first application discussed is predicting druggability, i.e., the ability of a site of binding druglike ligands with sufficient affinity.

Dr. Vajda applied the method to a large set of proteins. Results showed that because the method is based on the biophysics of binding rather than on empirical parameterization, meaningful information can be gained about classes of proteins and classes of compounds beyond those resembling validated targets and conventionally druglike ligands. In particular, the method identifies targets that, while not druggable by druglike compounds, may become druggable using compound classes such as macrocycles or other large molecules beyond the rule-of-five limit; proteins are classified according to their druggability. Second, hot spots provide crucial insights into the prospects for successful application of fragment-based drug discovery (FBDD), and whether a fragment hit can be advanced into a high affinity ligand. The key factor is the strength of the top ranking hot spot, and how well a given fragment complements it. Published data are sufficient to provide a sophisticated and quantitative understanding of how hot spot strength, number, and spatial arrangement govern the potential for a surface site to bind to fragment-sized and larger ligands. This improved understanding provides important guidance for the effective application of FBDD in drug discovery.

WEDNESDAY, December 9

Markovian Milestoning MD Simulations for Computing On- and Off-Rates
Cameron Abrams (Drexel University)
Molecular dynamics simulations have the potential to provide atomic-level detail and insight to important questions regarding the binding and unbinding kinetic predication. However, algorithms for estimating on- and off-rates remain undeveloped. In this talk, Dr. Abrams demonstrated how to apply Markovian milestoning along minimum-free energy pathways to establish transition rates for two systems: diffusion rates of CO inside Mb and MSOX. This method uses Voronoi tessellations, where the edges of Voronoi cells are used as milestones, and the necessary kinetic information about the transitions between the milestones is calculated by running molecular dynamics. Like the traditional milestoning technique, this procedure offers a reduced description of the original dynamics and permits to efficiently compute the quantities necessary. The method is able to successfully confirm experimental findings that histidine gate pathway is a major entry and escape route for CO inside Mb. It also supports the modified pin-pong mechanism in which oxygen reacts with E-red in MSOX.

Challenges in rational drug discovery - From drug binding to drug bioavailability
Chris Chipot (University of Illinois at Urbana-Champaign)
Accurate prediction of standard binding free energies describing protein−ligand association remains a daunting computational endeavor. Two distinct avenues to determine the standard binding free energy are compared. The first is direct calculation of the potential of mean force and the second invokes a series of geometrical restraints acting on collective variables designed to alleviate sampling limitations inherent to classical molecular dynamics simulations. The two distinct avenues to determine the standard binding free energy are compared in the case of a short, proline-rich peptide associating to the Src homology domain 3 of tyrosine kinase Abl. Both strategies yield nearly identical standard binding free energies with chemical accuracy. The prediction of bioavailability

comes with additional challenges. Bayesian inference is used to estimate the permeability of the biological membrane to a drug candidate, estimating the free energies and position-dependent diffusion coefficients along complex reaction coordinates form molecular dynamics simulation trajectories. Performance of the method is illustrated with prototypical permeants diffusing in a homogeneous lipid bilayer.

Correcting Free Energy Expressions for Thermal Motion
Martin Goethe (University of Barcelona)
In principle, the equilibrium state of a protein in solution can be identified from the minimum of a suitable free energy function. In practice, however, finding an accurate expression for the free energy function is a difficult task, not to mention the subsequent challenge of computing its minimum. Dr. Goethe investigated whether vibrational entropy (VE) is an important contribution to the free energy of globular proteins at ambient conditions. A term accounting for the VE of the protein was devised and existing potentials for the "thermal smoothing effect" were corrected. First, VE is measured explicitly for six different conformations from simulation data of a test protein. Estimates are obtained using the quasi-harmonic approximation for three coordinate sets, Cartesian, bond-angle-torsion (BAT), and a new set termed rotamer-degeneracy lifted BAT coordinates by us. The new set gives improved estimates thought the obtained VE values depend considerably on the type of coordinates used. Second, the thermal smoothing effect is when time-averaged potentials of proteins are smoother when expressed in terms of the average atom coordinates than the Hamiltonian. The strength of this effect varies greatly between atoms. To account for this effect, atom species are subdivided by their typical fluctuation behavior inside proteins. Time-averaging potentials for the new sub-species are also assigned, increasing the accuracy of free energy expressions.

Exploiting Active-site Water Structure and Thermodynamics for Drug Discovery and Design
Tom Kurtzman (City University of New York)
Despite recent advances in methodologies that better characterize local water structure and thermodynamics, the simply-stated question of whether it would be beneficial or detrimental, in a free-energetic sense, to displace water from a region of a protein with a suitably complementary ligand continues to be a conundrum. Models such as the iceberg model investigate the structure of water at interfaces. There are various ways in which water structure formation is sub-optimal. Inhomogeneous solvation theory can be used to estimate entropy. Solvation thermodynamic mapping techniques have provided valuable insight into the role of displacing water in molecular recognition; however, solvation thermodynamics alone is not predictive of displaceability, and tightly binding ligands regularly displace water from both regions that are characterized as having favorable solvation and regions that are characterized as having unfavorable solvation. Part of the difficulty of assessing the thermodynamics of water displacement is due to the large number of often counteracting contributions and the consequent lack of a simplifying conceptual framework. Key insights that have been gained from solvation thermodynamic mapping are presented, along with methods by which they are incorporated into drug discovery and design methodologies. Remaining issues on predicting favorability of water displacement and suggestions on how they might be tackled are presented.

In silico *design of a pain relief drug*
Christof Schütte (Freie Universität Berlin)
This presentation featured Markov State Modelling, a molecular dynamics coarse graining technique that has attracted a lot of attention in physical chemistry, biophysics, and computational biology in recent years. First, the key ideas of the mathematical theory behind Markov State Modelling and of its algorithmic realization were explained. Conformation dynamics can be modeled as a Markov process, focusing on kinetics and timescales. The transfer operator was presented as the evolution of reversible dynamics through the Fokker-Planck equation, and was used to determine long-term behavior of the system. The question of how to apply Markov State Modelling to understanding molecular function was discussed next. Finally, the question of whether this may help in designing molecules with prescribed function was investigated. All of this was illustrated through the story of the design process of a pain relief drug without concealing the potential pitfalls and obstacles. Results from the method's application to the pH-dependent opioid F-Fentanyl were presented, which has resulted in a patented drug.

THURSDAY, December 10

New Advances in Local and Nonlocal Electrostatic Modeling and Calculation for Ionic Solvated Biomolecules
Dexuan Xie (University of Wisconsin)
Calculation of electrostatics for a biomolecule (or a complex of a protein with a drug molecule) in an ionic solvent is a fundamental task in the fields of structural biology, computational biochemistry, biophysics, and mathematical biology. The Poisson-Boltzmann Equation (PBE) is one commonly used dielectric model for predicting electrostatics of ionic solvated biomolecules. In general, it can be used to formulate an implicit solvent model; many software packages for its implementation exist. The PBE has played an important role in rational drug design and protein design as well as other bioengineering applications. There are a number of challenges in solving the PBE, however, and it is known to not work properly near a highly charged biomolecular surface, since it does not reflect any polarization correlation among water molecules and ionic size effects.

To improve the quality of PBE in the calculation of electrostatic solvation and binding free energies, much progress has been made on the study of nonlocal dielectric models, and several fast nonlocal model solvers have been developed. The classical linear model is presented first, followed by the classic Poisson dielectric continuum model. Next, several nonlocal solver methods are presented, including the Fourier-Lorentzian model. Numerical algorithms for solving PBE and one size modified PBE include those using finite element, finite difference, solution decomposition, domain decomposition, and multigrid methods.

A Mathematical Introduction to Binding Free Energy, Enthalpy and Entropy
Michael Gilson (University of California San Diego)
Protein-ligand binding can be modeled with equations that are understood. The thermodynamic signatures of this binding show results from the change in average temperature, indicating that some energies are enthalpy-driven, others are entropy-driven,

and others are mixed. The standard free binding energy is the difference in chemical potential. The chemical potential is the difference between free energy of solvent molecules and the free energy of the solute; equations for calculating this are presented. In an ideal solution, the solvation free energy for solute can be isolated. A number of binding approximations and methods are available, including fast docking energy functions, mining minima, and double-decoupling. Similar theory can be applied to obtain the binding enthalpy, which is the difference in partial molar enthalpies. This formulation gives rise to a Boltzmann distribution. The binding free energy is equivalent to the reversible work.

The attach-pull-release method is presented next, followed by a discussion on how to obtain reliable calculations, which involves the use of advanced graphics processing units. Functional forms for non-polarizable force fields are shown, but simulation data needs to be validated against experimental data, such as pure liquid properties, small hydration data, and protein-ligand binding thermodynamics. Results comparing simulation and experimental data are shown, noting that uncertainties arise from blocking analysis and resampling. Host-guest systems can be useful in calculating force fields, and this leads to improved accuracy in drug design. Mathematical issues in these calculations include adjustment of parameters and accuracy estimates of predictions based on force fields.

The entropy associated with protein and ligand motion is presented next. In theory, this is calculable, but it is difficult in practice. It is shown how to construct a first-order approximation of entropy, noting the assumptions that are necessary (e.g., correlations are neglected). However, correlation is important, as it reduces entropy. Assuming that motions are not correlated, NMR can be used. To incorporate correlation, the mutual information expansion can be used, which is a Kirkwood-like superposition approximation. A number of statistical methods for measuring entropy are presented.

Revealing Structural Dynamics of GPCR Signaling through Atomic-level Simulation
Ron Dror (Stanford University)
G protein-coupled receptor (GPCR) signaling is introduced, noting the advancements that have been made in understanding this process in recent years. The first theme to be introduced is that allosteric binding is symmetric, particularly in its mathematical formulation. The derivation of this mathematical conclusion is presented. The binding process is the first step in understanding GPCR signaling, and spontaneous drug binding can be simulated, and these simulations result in a final pose that matches crystal structure. In particular, allosteric modulator binding is presented, though this doesn't result in a crystal structure. However, the bound pose does agree with mutagenesis data. Similar simulations were run for structurally diverse allosteric modulators; experimental results show that the main effect of allosteric modulation is to modulate the affinity of orthosteric ligands. Simulations allow investigation of why this effect occurs. Reasons include the electrostatic interaction between ligands and the coupled conformational change of orthosteric and allosteric sites. This insight aids the design of an allosteric modulator, which is validated experimentally. The second phase of GPCR signaling is activation.

Spontaneous inactivation is shown to arise naturally in unbiased simulations. Finally, the question of how a GPCR triggers G protein signaling is investigated. GPCRs cause GDP dissociation from the G protein, which causes GTP to bind to the G protein,

resulting in a downstream signaling cascade. Published literature shows that in G protein crystal structures, two domains (Ras and helical) sandwich the GDP. In GPCRs, this structure is substantially different. In the absence of receptor, domains frequently separate; in the GPCR, GDP remains bound even when one of the domains is removed. Nucleotide removal shows greater domain separation, more closely matching the receptor-bound crystal structure. Simulation results suggest that in order to cause rapid GDP release, the GPCR must weaken the affinity between GDP and the Ras domain. Ideas on automatically detecting important conformational changes are presented; performance comparisons are presented as well.

The design of protein switches
Ron Elber (University of Texas)
Proteins evolve as a sequence of point mutations of functional proteins that can be represented as a sequence of meaningful words. Sequences evolve within protein folds, which are essentially fixed and disconnected. Between animal species, sequence and structure identity remains as high as 85%, and as high as 20% between plant and animal. If enough point mutations occur, protein structures may change their fold or lose their function. During evolution, structures are better conserved than sequences. Sequence capacity and flow are of particular interest, as we can ask how many sequences are compatible with a given structure, and whether or not there is flow of sequences between structures under point mutations. Special protein pairs can switch their fold following a single point mutation. These proteins are of special interest since they offer a way to dramatically affect protein function. They also offer pathways for the evolution of protein structures. Special algorithms are required to explore the exponentially large space of protein sequences (in the sequence length) that may lead to a switch. Native sequences in their native fields can be examined according to their temperature distribution, and subsequently organized by sequence capacity and flow. The algorithms are described, as well as a detailed examination of a protein switch that was investigated experimentally and the construction of a network of protein switches. A network consisting of 3 nodes is presented as well, examining the protein evolution across multiple fold classes by stepwise mutation.

FRIDAY, December 11

Graphical Models for Drug and Protein Design
Christopher Langmead (Carnegie Mellon University)
Graphical models are data structures capable of encoding multivariate probability distributions, where nodes represent random variables and edges encode physical and/or statistical couplings. There are a variety of applications for graphical models. Several packages have been created focused on drug design, including two named Gremlin and Gerbil. A running example is introduced in which we want to learn a model from a multiple sequence alignment (MSA) of some protein. Column-wise conservation can be encoded with multinomial functions (node potentials) and coupling is described by edge potentials; this formulation is known as a Markov Random Field.

Gremlin (Generative regularized models of proteins) is an algorithm for learning the connectivity and parameters from MSAs, presented in the form of a discrete Markov random field. The algorithm is computed in polynomial time, and more importantly, it is consistent (meaning that it is guaranteed to converge given enough time). By using a regularized model, resulting models tend to be sparse, which is an advantage. Gremlin can be used to guide protein structure prediction as well as in the design of new sequences. These models perform better than standard PFAM models, and the improvement increases dramatically with sequence length. Gerbil is an extension of Gremlin focused on modeling higher-order couplings. This has shown an improvement on traditional models by as much as 38 percent.

Models can be combined by adding inter-molecular edges in order to investigate protein-protein interactions. The PDZ domain is used as a running example to highlight how the algorithm DGSPI works. An interaction matrix is formed that incorporates both known interactions and non-interactions. A regression model is used on intra-molecular dynamics.

Quantifying the influence of conformational uncertainty in biomolecular solvation
Huan Lei (Battelle Pacific Northwest Laboratories)

The environment of a biomolecular solution is important. Free energy and potential mean force can be calculated given a particular solvent, and the role of solvent on solute can be investigated. A number of solvation models have been formulated, and many rely on the Poisson-Boltzmann equation (PBE). Continuum methods allow a high degree of accuracy; however, there are several issues. Calculating polar and non-polar interactions in the same solvent is an open problem. Additionally, the PBE fails in cases of high charge density. Biomolecular conformation fluctuates because the biomolecules are not rigid, but Monte Carlo sampling is too computationally expensive to fully investigate the space. The approach here is to construct a sample model for the full space. Numerical challenges include the high dimensionality of the space and the sampling error from data.

A stochastic model can be constructed based on harmonic potentials. The quadratic approximation leads to a Gaussian distribution for conformational fluctuation that can be used to generate individual residues. The dimensionality of the stochastic model can be reduced in certain cases if the correlation matrix is partially known. Polynomial chaos is used to represent the uncertainty in the system, and a distribution can subsequently be derived. It is shown how coefficients for the polynomial chaos expansion can be calculated and how the sparsity of the expansion can be increased. Iterative rotation is used to improve surrogate models, resulting in greater sparsity. However, the sparse grid method is sensitive to numerical error; addressing this issue is an idea for future work.

Targeting disease-causing effects with small molecules binding
Emil Alexov (Clemson University)

DNA mutations are the cause of many human diseases and they are also the reason for natural differences among individuals by affecting the structure, function, interactions, and other properties of DNA and expressed proteins as well as protein-protein interactions. Some diseases are caused by mutations in several genes, while others are caused by defects

in a single gene (monogenic diseases). The free energy changes in folding and binding can be calculated using a variety of methods. A webtool has been made available to perform these calculations. A benchmarking protocol has been developed to provide estimates on the errors of the calculations. Applications are focused on two monogenic diseases: (a) the Snyder-Robinson Syndrome (SRS) which is a rare mental retardation disorder caused by missense mutations in spermine synthase (SMS) and (b) the Rett syndrome (RTT) which is a brain disorder that is linked with mutations in the MeCP2 protein, and it is estimated to affect 1 in 8,500 females.

Little is known about the MeCP2 protein. In RTT, most of the mutations occur in the MBD domain. The vast majority of mutations do not directly affect the functionality of the corresponding protein, but rather alter its stability and affinity. This prompted us to seek small molecules that target the mutant protein and upon the binding restore its wild type characteristics. Out of 24 ligands investigated, 10 were identified for testing. Results show that these ligands are promising drug targets as it may be possible to restore binding rates to those of the wildtype.

Several substrates are identified as necessary for normal brain function with regards to SMS, which is known to be highly charged. Experiments were carried out to verify dimer affinity. The modeling protocol was applied in order to identify binding pockets. Experimental results are shown indicating the malfunctioning SMS mutants that were rescued.

Spring Workshop 1 - Dynamics in Networks with Special Properties (January 25-29, 2016)

Organizers: Pete Ashwin (University of Exeter), Tomas Gedeon (Montana State University), and Gheorghe Craciun (University of Wisconsin-Madison)

Report by: Karly Jacobsen, Leili Shahriyari, Min Wang

MONDAY, JANUARY 25, 2016

Nontrivial collective dynamics in a network of pulse-coupled oscillators
Antonio Politi (University of Aberdeen)
Dr. Politi explained how an ensemble of mean-field oscillators characterized by different frequencies could exhibit a highly complex collective dynamics. He presented an example where the phase-response curve is obtained by smoothing out the response of delayed leaky integrate-and-fire neurons. The speaker showed that the microscopic dynamics are linearly stable, and the global (macroscopic) evolution is irregular (high-dimensional). The speaker then mentioned that this phenomenon poses the question of how the two levels of description are actually connected.

Data mining the Kuramoto Equations on Cubic graphs
Bard Ermentrout (University of Pittsburgh)

Dr. Ermentrout started his talk by introducing cubic graphs. He then talked about high-energy patterns. He used Monte-Carlo methods to obtain the patterns. He described the dynamics of a system of sinusoidally coupled phase oscillators on cubic graphs. He mentioned that the synchronous solution is always an attractor. However, as the graphs get larger (more nodes), it is possible to get other stable attractors. He also described the energy and degree of stability of these non-synchronous attractors for some cubic graphs. He used some techniques from computational algebraic geometry to show that for some graphs, the only attractor is synchrony.

Weak chimera states for small networks of oscillators
Peter Ashwin (University of Exeter)
At the beginning of the talk, Dr. Ashwin defined oscillator networks and weak chimeras. He then stated various definitions for chimera. He asked two following questions: "what are the limits on how small a network can be to have chimeras?" and "are there any limits on stability of chimeras in small networks?" He then provided some examples for modular networks. He also presented examples for six and ten oscillators, and explained their differences. The speaker then mentioned six oscillator networks without modular structure. Finally, he mentioned future work: scaling of weak chimeras to chimeras in continuum limit, and Fred desynchronization in non-modular networks.

Noise and intelligence in intracellular gene-regulatory networks
***A*lexey Zaikin (University College London)**
Dr. Zaikin began by defining intelligence and talking about history of artificial intelligence. He then stated the principles of artificial neural network. The speaker also explained the one-layer feed-forward neural network and a Hopfield network. After that he described a mathematical model for the transcriptional regulation, a system of equations that models dynamics of mRNA and protein. Dr. Zaikin said he is interested in modeling noisy genetic regulation system, because gene expression is an intrinsically noisy process. Therefore, he talked about the effect of intrinsic and extrinsic noise on intracellular intelligence.

A proof of the Global Attractor Conjecture: global stability and robust permanence
Gheorghe Craciun (University of Wisconsin-Madison)
The speaker first defined the global attractor conjecture by explaining mass-action kinetics. He claimed there is a one-to-one correspondence between the nonlinear reaction system of equations and geometrically embedded graphs. He then stated the Horn-Jackson Theorem (1972): if a reaction system is vertex balances then there exists a strict Lyapunov function within each linear invariant subspace. After that, he stated the Horn conjecture (1974): if a system is vertex balanced, then it has a globally attracting point within each linear invariant subspace. He mentioned several special cases of this conjecture have been proved during the last decade. The speaker described a proof of the conjecture in full generality. Finally, he concluded that all detailed balanced mass action systems and all deficiency zero weakly reversible networks have the global attractor property.

Properties of Solutions of Coupled Systems
Marty Golubitsky (The Ohio State University)

Dr. Golubitsky began by explaining how networks of equations can be defined by directed graphs, and how to use network architecture to discover rigid synchrony, rigid phase-shift synchrony, and unusual bifurcations. He asked the following question: Which properties of solutions of coupled equations follow from network architecture? Answers include "patterns of synchrony" for equilibria and "patterns of phase-shift synchrony" for time-periodic solutions. He defined a coloring to be *balanced* if all nodes with the same color receive the same number of colored inputs. He then stated a theorem that a pattern of synchrony is rigid if and only if it has a coloring that is balanced. Further, he mentioned that balanced colorings always lead to quotient networks and that a transitive network has non-zero rigid phase-shift synchrony if and only if there is a phase-shift forced by symmetry on the quotient network. Golubitsky also presented models for binocular rivalry. He defined Wilson networks for generalized rivalry and showed how Wilson networks predict the correct set of observed percepts in Kovacs *et al.* binocular rivalry experiments. The speaker ended by discussing how homeostasis can be viewed as a network phenomenon.

TUESDAY, JANUARY 26, 2016

Evolution of gene networks in fluctuating environments
Stephen Proulx (University of California, Santa Barbara)
In this talk, Dr. Proulx discussed how gene networks evolve in response to variability in the environment. He began by introducing general approaches on modeling evolution of gene networks. He then described the central-dogma diagram and used it as a framework to explain what the transcription control is in transcription control networks. Dr. Proulx also showed a dynamic model of single gene regulation in response to two environment states and occasional shift between states. The long term behaviour of gene expression in this model was calculated and the fitness consequences of changes was determined in the gene regulation. He then embedded this model into a population genetic framework in order to determine the conditions that allow populations to evolve environment-specific transcription rates. Furthermore, Dr. Proulx incorporated Hill functions to model the effect of concentration of the transcription factor in different scenarios, which can describe gene interaction and predict evolutionary outcome. The optimal control strategy to the models of the gene expression was also compared to the evolved gene network model under a variety of regimes. Finally Dr. Proulx concluded that the pure transcription factor gene can help improve the evolved network fitness when information storage or process is useful.

Applications of Generalized Networks to Biochemical Reaction Systems
Matthew Johnston (San Jose State University)
Dr. Johnston discussed some recent applications of generalized network theory to determine the dynamical properties of biochemical reaction systems. He started by introducing the mass action systems with two specific examples on protein activation and MAPK cascade models. He then summarized the properties of the general mass action systems which essentially track the concentrations with system of polynomial differential equations. Dr. Johnston mentioned the deficiency zero theorem which studies the equivalence between balanced system dynamics and the network properties. He noted that

this theorem applies for one of the previous two examples while it fails for the other one. Dr. Johnston finally presented dynamically equivalent but better structured generalized networks with two sets of complexes for these two examples. The generalized mass action systems have the advantage on some of the properties, but Dr. Johnston also pointed out that the information of other properties are lost in the framework of this generalized network.

Model for Cholera Dynamics on a Random Network
Pauline van den Driessche (University of Victoria)
Dr. van den Driessche began with an overview of cholera, including death rate, occurrence, and transmission pathways. She aimed to model the spread of cholera by adapting the Miller model on a network. She modeled the person-to-person contacts by a random contact network, and added the contagious environment as an external node that connects to every individual which accounts for the waterborne disease dynamics. There are now two pathways in this model: the person-to-person and person-to-water-to-person pathways. With certain assumptions included, a system of equations were established which give the full network model with initial conditions. Dr. van den Driessche then analysed the network model and computed the basic reproduction number R0. She investigated the conditions under which cholera dies out or becomes epidemic. The dynamics of her model showed excellent agreement with stochastic simulations. Finally a Poisson network was proposed and shown to be the sum of the basic reproduction numbers of the two pathways, as in the homogeneous mixing limit of the transmission compartment model.

Synchrony in networks of coupled non smooth dynamical systems: Extending the master stability function
Stephen Coombes (University of Nottingham)
Dr. Coombes began by describing two examples on piecewise linear (pwl) dynamical systems. The first example is a nice system which is broken by a switching manifold into two parts with a stable period orbit going around a non-stable fixed point. The other system is the Mckean model of an excitable system that has been extensively studied in the mathematical neuroscience community. He demonstrated that considerable insight into network dynamics can be obtained when choosing the dynamics of the nodes to be pwl. To determine the stability of the synchronous state in terms of the eigenstructure of the network, Dr. Coombes discussed the extension of master stability function to these non-smooth planar pwl systems. He described an inverse period-doubling route to synchrony, under variation in coupling strength, in linearly coupled networks for which the node dynamics is poised near a homoclinic bifurcation. Dr. Coombes also contrasted this with node dynamics poised near a non-smooth Andronov-Hopf bifurcation and a saddle node bifurcation of limit cycles, for which no such bifurcation of synchrony occurs.

Which reaction networks are multistationary?
Anne Shiu (Texas A&M University)
In this talk, Dr. Shiu presented multiple criteria that can be used to determine if a given chemical reaction network admits multiple steady states. She first mentioned well-known results on deficiency and injectivity as criterion for multistationarity. The next criterion

presented was a lifting result, motivated in biology in the scenario of small graph motifs in a larger network, G. If the small network is multistationary then G is multistationary if the small network is either a particular class of subnetwork embedded in G or an induced network formed by removing intermediates. The goal of the work was to start creating a catalogue of small multistationary networks which can be used to determine if larger networks are multistationary. Reaction diagrams (Newton polytopes) were employed in the analysis. She presented a theorem for 2 species and 2 non-flow reactions and found exactly 11 embedding-minimal multistationary networks. The main theorem was for s species and r reactions. Dr. Shiu presented an example where a subnetwork of a bistable apoptosis network was multistationary but an autocatalytic network was not.

Statistical inference in a chemical soup
Manoj Gopalkrishnan (Tata Institute of Fundamental Research)
Dr. Gopalkrishnan focused on computation using chemical reaction networks and statistical inference as a high level model of computation native to reaction networks. In particular, he presented a recipe for computing the maximum likelihood distribution (MLD) of a log-linear model using reaction networks. The algorithm takes the design matrix, computes the basis of its kernel, corresponds each basis element to a reversible reaction and applies mass-action kinetics with unit rates where the initial conditions are determined from frequency data. The main theorem stated was that the equilibrium point is the MLD with global convergence to this equilibrium. The result follows from the facts that the MLD maximizes the Shannon entropy subject to a constraint, mass-action kinetics maximizes entropy and the maximizer is unique. He concluded with a discussion of the limitations due to high dimensional design matrices and the possibility of using graphical models to represent a high dimensional system.

A patched Ross-Macdonald malaria model with human and mosquito movement: implications for control
Patrick DeLeenheer (Oregon State University)
Dr. DeLeenheer presented a multi-patch model for malaria where the dynamics in each patch were determined by a simplified Ross-Macdonald model including an incubation period. To take account of environmental heterogeneity, each patch was characterized by its own basic reproduction number and the infection rate of susceptibles was an average of infection rate across the patches weighted by the proportion of time spent there. He presented a result giving a dichotomy for convergence to either a disease-free or endemic steady state based on the spectral radius of a matrix involving the patch residence times for mosquitos and humans. He then considered whether vector sources and sinks could be reconstructed, given the endemic equilibrium for the human population, and what additional information would be needed. He concluded with a discussion of control of infection on natural landscapes and the success or failure of certain strategies based on the movement patterns exhibited by hosts and vectors.

Dynamics of multisite phosphorylation
Stanislav Shvartsman (Princeton University)
Dr. Shvartsman gave a lecture via video on the analysis of long-term dynamics in a model with multiple phosphostates and tunable processivity. The problem arises from

consideration of inductive signaling in embryos, particularly in the ERK (extracellular signal regulated kinase) signaling pathway. Developmental abnormalities, such as craniofacial malformations and heart defects, can be caused by deregulated ERK signaling. As resolved experimentally by mass spectrometry, the relevant enzyme can be in four possible states, depending on whether it is phosphorylated at each T and Y site. Phosphorylation and dephosphorylation are ordered and, thus, the minimal network to consider has two enzymes, four substrates and six reactions. The speaker presented models that contained fully processive and fully distributive mechanisms, in terms of the dissociative and catalytic reaction rates, as limiting regimes of a general model on the minimal network. He demonstrated that the model with varying processivity demonstrates bistability for varying parameters and can also manifest oscillations in which the model is essentially functioning in the distributive regime. He concluded by posing some questions of interest for the audience, asking if it possible to prove that a fully processive mechanism with four states has a unique steady state, what happens for small deviations from processivity, and if one can characterize the structure of oscillatory parameter sets.

Network motifs provide signatures that characterize metabolism of cellular organelles
Santiago Schnell (University of Michigan)
Dr. Schnell discussed the development of a computational methodology to infer physiological dysfunction from a metabolic network representation. The hypothesis was that network motifs capture relevant interspecies metabolic information that can be used to make inferences about similarity of metabolic function and ancestry. Motifs with three nodes were considered and FANMOD (fast network motif detection) was employed to identify all such motifs. They found that individual motifs are associated with a range of biochemical functions. They next investigated the network motif distribution (i.e. metabolic signatures) in different cellular organelles. Results indicated that the cytoplasm of all organisms has roughly the same distribution of motifs while organelles displayed distinct motif distributions with statistical significance. They focused on three primary branches: bacteria, archaea, and eukarya to investigate ancestry via network motif distributions. Their analysis demonstrated that the mitochondria appears most like a delta or epsilon proteobacteria. The speaker concluded by mentioning future work of using network enumeration approaches to map network motifs to behavior, pointing out that a major challenge is that typical network representation used by biologists is coarse-grained.

WEDNESDAY, JANUARY 27, 2016

Database for Dynamic Signatures of Gene Regulatory Networks: Theory
Konstantin Mischaikow (Rutgers University)
Dr. Mischaikow started by explaining what the phrase "a solution to a differential equation" means. He then explained the network lac operon model. He emphasized that ODEs are great modeling tools, but they must be treated with special care. He stated quantitative data is often subject to large uncertainty and is mostly in terms of fold differences. Thus, it is very difficult to make reliable predictions using the continuous models. Therefore, he developed a new method that uses continuous time Boolean networks. To justify this new approach, the speaker compared classical Morse theory and

Conley Morse theory. He also mentioned a corollary of Birkhoff's theorem: the Morse graph and the lattice of attractors are equivalent.

Database for Dynamic Signatures of Gene Regulatory Networks: Applications
Tomas Gedeon (Montana State University)
Dr. Gedeon began by introducing the typical models of gene regulatory. He took the Hill function model as an example and described the difficulties and drawbacks of it in making reliable predictions. Dr. Gedeon then proposed the computational switching model with the Morse set defined in the Morse graph and showed its advantages to the typical models by going through an example. More details were given about the Morse graph, and the mechanism by which the Morse graph tells about the combinatorial dynamics was interpreted and verified by a theorem. Dr. Gedeon also discussed the applications of a database called DSGRN for dynamical signatures of gene regulatory networks. He proposed two approaches to compare the output of this database procedure to data. Finally Dr. Gedeon used the malaria pacemaker network to validate that his database allows search for dynamics signatures and search for matches with experimental data.

Structural approach for sensitivity of chemical reaction networks
Atsushi Mochizuki (Theoretical Biology Laboratory, RIKEN)
Dr. Mochizuki discussed the structural theories to derive important aspects of the dynamical properties of network systems. That is, a mathematical method, named structural sensitivity analysis, is developed to determine the sensitivity of reaction systems from information on the network alone. He investigated how the sensitivity responses of chemicals in a reaction network depend on the structure of the network, and on the position of the perturbed reaction in the network. He then established and proved directly a general law which connects the network topology and the sensitivity patterns of metabolite responses. One theorem in his method also explains two prominent features of network in sensitivity: localization and hierarchy in response pattern. Dr. Mochizuki also applied his method to several hypothetical and real life chemical reaction networks, including the metabolic network of the E. coli TCA cycle. By his method, important aspects of the dynamical properties of the system can be derived from information on the network structure, only, without assuming other quantitative details. Dr. Mochizuki concluded that the theorem is useful, practically, when examining real biological networks based on sensitivity experiments.

Admissible circuits
Christophe Soule (Institut des Hautes Études Scientifiques)
Dr. Soule discussed the various conditions under which there exist admissible positive circuits on reaction graphs of gene networks. He started by presenting the Thomas rule for gene networks about the existence of a positive circuit whose condition is easily satisfied when it is applied to biochemical networks. Dr. Soule then described Soliman's theorem whose result condition is stronger than that in Thomas' rule. He explained that the influence graph must contain an admissible positive circuit by looking at a simple example. Dr. Soule went on to talk about his joint work with M. Kaufman, and they found a new condition which is stronger than the one of Soliman's. Finally he gave two examples --- the

Brusselator and a system of specific reactions with computed Jacobian matrix to verify his findings.

Trust in Network Analysis
Srinivasan Parthasarathy (The Ohio State University)
Dr. Parthasarathy discussed an ensemble clustering approach he recently developed which incorporates three topology-based similarity measures as a key component. He began by enumerating the challenges in analysing data in the current world full of noise and uncertainty. He went on to talk about the need for trustworthy analysis of protein-protein interaction networks. The idea of ensemble clustering, which is a useful approach to combine results from multiple clustering arrangement into a single arrangement, is then borrowed and offered as a natural solution to the above challenges. Dr. Parthasarathy also leveraged the topological information in network to determine the similarity metrics which are central to any clustering algorithm. Three types of similarity metrics, the clustering coefficient-based similarity, the edge betweenness-based similarity, and the neighbourhood-based similarity, are extensively introduced and explained with details. Then a statistical technique called logistic PCA is used as a dimensionality reduction tool. With the introduced metrics, base clustering algorithms, and dimension reduction tools, Dr. Parthasarathy built an ensemble framework for clustering biological networks. Furthermore he compared the developed ensemble algorithm with the other famous clustering approaches, and validated that his algorithm outperforms the others by checking the performance of them. Finally Dr. Parthasarathy described the broad applicability of the ensemble method to predict protein-DNA binding under stress dynamics, and concluded that the developed algorithm shows promise as unified method for trustworthy analysis of networks.

Multi-stationary in a MAPK network model
Maya Mincheva (Northern Illinois University)
Dr. Mincheva began by stating that MAPK networks are common part of intracellular networks. Then she explained what the AMPK network is. The speaker also defined multi-stability as the existence of multiple stable steady states. She mentioned that multistability is an important property of such networks. Dr. Mincheva explained a method to obtain parameter values for multi-stability for some models of MAPK networks. Note, deciding if a given model has the capacity for multi-stationarity (the existence of multiple steady states) usually requires an extensive search of the parameter space. Therefore, she stated a theorem that indicates if one specific inequality is satisfied, multi-stationarity, and hence the potential for multistability, is guaranteed. She also proved if another specific inequality is satisfied, the uniqueness of a steady state, and hence the absence of multi-stability, is guaranteed. The method also allows for the direct computation of the total concentration values such that multi-stationarity occurs. Finally, she talked about some possible generalizations of this method.

Effects of time-delay in a model of intra- and inter- personal motor coordination
Krasimira Tsaneva-Atanasova (University of Exeter)
The speaker started by explaining the importance of motor coordination as a feature of intra- and inter- personal interaction. She then described the finger tapping movement and

the Haken-Kelso-Bunz (HKB) model for this experiment. She developed a different approach, which systematically investigates the behaviour in the full system. She performed detailed numerical bifurcation analyses, and showed that the HKB model supports previously unreported dynamical regimes as well as bi-stability between a variety of coordination patterns. Moreover, the speaker explained the result of adding a delay in the coupling. Then she showed that the delay has a significant effect on the observed dynamics. In particular, she obtained a much larger degree of bi-stability between in-phase and anti-phase oscillations in the presence of a frequency detuning.

Emergence of collective behavior in coupled oscillator systems
Matthias Wolfrum (Weierstrass Institute)
Dr. Wolfrum began by providing an historical introduction on coupled oscillator systems and explaining the classical Kuramoto model (1965). He also stated the reasons that we need to study oscillators systems with complex parameters. Then he explained the Kuramoto-Sakaguchi model (1977), and the model developed by the speaker, which is the generalization of this model. He also talked about another new developed model that is an array of Kuramoto-Sakaguchi oscillators with non-local coupling. He discussed the properties of the solutions of these models.

In search of network-level respiratory burst synchronization mechanisms
Jonathan Rubin (University of Pittsburgh)
First, the speaker explained the respiratory system, and noted that there is a collection of neural population in respiratory brainstem. He discussed the pre-Botzinger complex (pBC) network, which maintains rhythmic oscillation, and its role in the mammalian brainstem. He explained the properties of single pBc neurons and their synaptic interactions. He also introduced Hartelt network developed in 2008. After that, he discussed a model, which was a collection of Hartelt networks. The speaker also presented some computational approaches to systematically study how burst synchrony depends on network properties. Furthermore, he talked about some analytical approaches to estimate impacts of the prevalence of architectural motifs on the spread of activity in a network, and some rigorous analysis of graphicality and graph enumeration that are relevant to testing the motif-based ideas computationally.

Atoms of multi-stationarity in reaction networks
Badal Joshi (California State University, San Marcos)
Dr. Joshi defined the Glycolysis network, and he focused on multi-stationarity and the properties that can be fined on sub-networks, which could be extended to the whole network. He mentioned that identifying reaction networks that admit multiple positive steady states is an open problem. Criteria such as deficiency theory and Jacobian criterion help rule out the possibility of multiple steady states. However, these tests are not sufficient to determine multi-stationarity. For fully open networks, he could establish multi-stationarity by relating the steady states of a reaction network with those of its component "embedded networks". He referred to the multi-stationary fully open networks that are minimal with respect to the embedding relation as atoms of multi-stationarity. He identified some families of atoms of multi-stationarity and showed that there exist arbitrarily large (in species, reactions) such atoms.

Extending Levelt's propositions to perceptual multistability involving interocular grouping
Yunjiao Wang (Texas Southern University)
The speaker began with an introduction to binocular rivalry in which percepts are rivaling between two presented images. She introduced the influential 1965 work by Levelt on binocular rivalry and an updated 2015 version for bistable perceptual rivalry describing relations between strength of stimulus, dominance duration and predominance. The work of Dr. Wang and her colleagues extends the Levelt propositions to multistable perceptual rivalry. An experiment was performed with single eye and interocular grouping percepts that used color saturation as a factor for manipulating percept strength. Results indicated that dominance duration distributions follow a gamma distribution, predominance of grouped percepts increase as the color saturation level increases and dominance duration of single-eye percept decreased while that of grouped percepts remained relatively unchanged. All results were consistent with the first three of the generalized Levelt propositions. She then presented a network model with coupling and feed-forward excitation in order to determine what mechanism was responsible for the behavior. She finally presented dynamics of the deterministic model at the lower level with four nodes. The fast system has four stable steady states in some parameter range and the switches are driven by both adaptation and noise.

The Kuramoto model on Cayley and random graphs
Georgi Medvedev (Drexel University)
Dr. Medvedev began with an introduction to connectivity in random graphs including Cayley graphs, k-nearest-neighbor graphs, Paley graphs, quasirandom graphs, and Erdos-Renyi graphs. He considered large, dense graphs for which a formal tool for describing the asymptotic behavior has been developed by Lovasz et al. He presented a theorem about convergence of dense graph sequences and a corresponding geometric interpretation in terms of pixel pictures. The main question of his talk asked if, given graphs with the same asymptotic properties, a dynamical system on the graphs will have the same behavior? The Kuramoto model, a prominent model of coupled phase oscillators, on a Cayley graph was considered. He focused on the complete graph in a repulsive coupling case in which all twisted states are stable. The same analysis was performed for the Paley graph and it was found that there exists a twisted state that is unstable for the repulsive coupling case. He concluded by presenting a theorem for models on an Erdos-Renyi graph indicating that an average model approximates solutions to original models with large probability on finite time intervals.

Some aspects of injectivity and multistationarity in networks of interacting elements
Casian Pantea (West Virginia University)
Dr. Pantea first gave an introduction to chemical reaction network kinetics with mass-action as well as general kinetics in which the exact form of the rates is not known. The remainder of the talk focused on the existence of multiple equilibria for some stoichiometric compatibility class. A condition for injectivity of the vector field was

presented in terms of the sign pattern and sign-nonsingularity. He presented a rank condition for injectivity based on a matrix determined by the structure of the network and presented a concordance condition that used a reduced determinant. A toy example was used to demonstrate that the sign compatibility condition has a nice interpretation in graph theory.

Some combinatorial and algebraic problems arising from the study of chemical reaction networks
Murad Banaji (Middlesex University)
Dr. Banaji talked about how questions about chemical reaction networks (CRN) lead to interesting and rich theory in combinatorics and algebra. The speaker began with an introduction to sign nonsingularity (SNS) as an example of combinatorial analogs to linear algebra questions, giving the example of a bipartite graph as a zero matrix. SNS is a combinatorial property which can be expressed equivalently in terms of the weighted bipartite graph being centrally 2-odd. Dr. Banaji continued with a brief overview of CRN theory mentioning that some results (e.g. injectivity) are robust to switching reactions and species. He gave some examples of how decision problems about matrix-sets arise, such as those concerning the r-determinant, bijectivity of the Jacobian and the spectrum avoiding some set in the complex plane. Finally, the speaker concluded with a brief discussion of spin-offs concerning products of sign-patterns, including a result that characterized forests by looking at products of associated sign pattern matrices.

A model framework for transcription-translation dynamics
Roderick Edwards (University of Victoria)
The speaker began with an overview of gene regulation and qualitative models that assume transcription factors directly regulate the expression of other transcription factors, without intermediate variables. In particular, he discussed nonlinear models using sigmoidal regulation functions that become Glass networks in some limit. He alternatively presented a model with two variables (mRNA and protein concentrations) per gene that explicitly tracks both transcription and translation dynamics. The focus of the talk was then on the extension of the Glass network type analysis to these transcription-translation networks. The method for analysis was the creation of a pseudo-state transition diagram and the use of pseudo-thresholds for mRNA variables to define pseudo-state domains. The resulting flow across edges was then uniquely oriented, which facilitated analysis. He concluded with a result for negative feedback loops: in a certain limit there exists a qualitative cycle for a negative monotone feedback loop if and only if the thresholds are in an appropriate range.

Steady states of MESSI biological systems
Alicia Dickenstein (University of Buenos Aires)
Dr. Dickenstein presented a general framework for biological systems that describe Modifications of type Enzyme-Substrate or Swap with Intermediates (MESSI). Examples of MESSI systems include processive phosphorylations, phosphorylation cascades and enzymatic networks with different architectures. Assuming mass-action, the study of steady states and conservation laws of these systems are simplified by elimination of intermediate complexes. A theorem was presented which stated that a

MESSI system has one independent linear conservation relation associated to each of the subsets in the partition of the species set corresponding to non-intermediate species. A second theorem was given for conservation relations: if the partition is minimal with no swaps, and each connected component has only one terminal strong linkage class, then all the conservation relations are linearly generated by defined conservations. The speaker concluded by identifying a class of networks, those corresponding to a linked MESSI system, in which many results follow straightforwardly including existence of toric steady states, conditions for persistence, and the occurrence of multi-stationarity.

FRIDAY, JANUARY 29, 2016

Basic Bifurcation Theory for Neural Networks --- CPGs
Andrey Shilnikov (Georgia State University)
Dr. Shilnikov discussed the development of a practical bifurcation for small network models, especially the networks of cells called central pattern generators (CPG), which generate several bursting patterns at various time scales. A CPG is a neural microcircuit of cells whose synergetic interactions can automatically produce an array of multicomponent/polyrhythmic bursting patterns of activity that control behaviors. Dr. Shilnikov gave several examples to show that CPGs have been identified and studied in animals where they have been implicated in the control of diverse behavior rhythms such as swim, walk, sleep, heartbeat, respiration, chewing and locomotion. Dr. Shilnikov and his collaborators explored how observed multi-stable stables arise from coupling and how real circuits may take advantage of multi-stability to dynamically switch between the corresponding polyrhythmic outputs. They further studied the repetitive dynamics generated by constituent building blocks or "motifs" that make up more complex CPG circuits, and the dynamic principles underlying more general multi-stable rhythmic patterns. Dr. Shilnikov also developed a novel dynamical and bifurcation framework combining analytical approaches and computational tools to in-detail study oscillatory networks constituted by endogenously bursting or tonic spiking neurons and network busters. Furthermore he identified and described key qualitative rhythmic states in various 3-cell, 4-cell and coupled network motifs of multifunctional CPGs, which provide a systematic basis for understanding plausible biophysical mechanism for the regulation of rhythmic patterns in the context of motor control. Finally Dr. Shilnikov concluded that his analysis provides a powerful qualitative approach to study detailed models of rhythmic behavior, and this approach is applicable to a wide range of biological phenomena beyond motor control.

Species Composition and Reversibility in Chemical Reaction Network Theory
Gilles Gnacadja (Amgen)
Dr. Gnacadja began the talk by describing the need for augmentation to the current chemical reaction network theory. He then used examples for illustration which is helpful to derive the precise definitions for the fundamental sets: set of species, set of complexes, and set of reactions in standard reaction network. Dr. Gnacadja also proposed and developed a formal notion of species composition to account for the idea that species are composed of elementary units or building blocks. More notions including those associated

with a composition are defined and some trivial results are provided to illustrate these notions. Furthermore, Dr. Gnacadja was motivated by the augmented chemical reaction network theory with notion of phenomenological non-graph theoretic reversibility condition which defines a categorization of reactions, and then developed a theory of constructive networks and used it to apply the characterization of vacuous persistence. He obtained that a widely applicable reversibility condition along with the absence of isomerism among elementary species assure vacuous persistence. Finally Dr. Gnacadja formally defined binary enzymatic networks and proposed a theorem which shows that those mass action binary enzymatic networks that are futile and cascaded are vacuously persistent.

Stochastic Decoupling of Biomolecular Networks
Heinz Koeppl (Technische Universitat Darmstadt)
Dr. Koeppl discussed a general mathematical framework that allows to uncouple the network from its dynamic environment by incorporating only the environment's effect onto the network into a new model. He explained the motivation to find a "self-contained" mathematical model that summarizes all system behaviors attainable under all possible realizations of the extrinsic environment fluctuations. Such models could then be used to perform an uncoupled analysis of a reaction network subject to extrinsic noise which can help dissect measured variability into contributions from target network and environment. Dr. Koeppl then described that he found a mathematical correct answer which is to marginalize the system dynamics with respect to the extrinsic fluctuation. He showed how the fluctuating extrinsic components, for example, chemical species, are marginalized to obtain the decoupled model by illustrating three examples. Dr. Koeppl derived the corresponding process and master equations for continuous time Markov chains in generalized reaction network, and mentioned how the Monte Carlo simulations are performed. In the context of simulation the decoupled process can yield a significant reduction computational effort when compared to standard SSA. Finally Dr. Koeppl demonstrated the significance of the approach which provides a novel and orthogonal notion of environmentally perturbed stochastic network from which several interesting avenues could be pursued.

From motifs of regulatory networks to coupled stochastic systems
Fernando Antoneli (Universidade Federal De São Paulo)
Dr. Antoneli began by proposing and solving a hybrid model for single gene expression dynamics. It is analyzed by the associated master equation that describes the production of messenger RNA (mRNA) molecules triggered by this single gene with various levels of promoter activity. From another point of view, this model is approached as a Random Dynamical System (RDS). Dr. Antoneli then defined the basic building blocks called the 2-dimensional affine RDS with the corresponding dynamics --- discrete time hybrid model. He briefly examined the fundamental building block of gene regulatory circuits called external regulated genes which are the single gene with three different types of switching. He went on to show how to implement multiple gene regulation within the framework for three common network motifs. Dr. Antoneli also considered two genes with different state variables and a connected linkage, and provided the coupling between the two corresponding systems by an input function, which measures the concentration of a ligand

into binding affinity. The prominent examples of input functions is comprised by the Hill function family. Furthermore Dr. Antoneli introduced three logical gates and implemented these logical gates in his formalism by composing the input function with some appropriate operations at the level of concentrations. It is showed that under some conditions the "big" coupled system is RDS. Finally Dr. Antoneli interpreted and validated the model by simulating the typical time series and stationary distributions of the single gene dynamics and network motifs with various switching types.

Spring Current Topic Workshop 2 - Modeling and Inference from Single Molecules to Cells
(February 8-12, 2016)

Organizers: Jayajit Das (The Ohio State University), Ashok Prasad (Colorado State University), John Fricks (Pennsylvania State University), Steve Presse (Indiana University--Purdue University)

Report by: Márcio Mourão, Reginald McGee, Rajeev Azad

MONDAY, FEBRUARY 8, 2016

Physics of protein folding and its relation to evolution and cellular laws
Kingshuk Ghosh (University of Denver)
Dr. Ghosh started his presentation by describing and distinguishing traditional (one protein at a time) versus large-scale studies in protein science (collection of proteins). He explained how protein thermodynamics can be modelled using the free energy of folding and showed that both enthalpy (H) and entropy (S) linearly depend on the number of aminoacids in the protein. Using the folded state only, Dr. Ghosh explained how thermophiles withstand higher temperatures (from folded to unfolded) than mesophiles. His results show that thermophiles have less change in H and S than mesophiles and that thermophiles gain stability by reducing loss in S. Considering unfolded states as well, Dr. Ghosh modelled the protein-disordered state as a connected chain of aminoacids with excluded volume and electrostatic interactions. He applied his model to 540 real orthologous protein pairs from thermophilic and mesophilic proteomes and concluded that thermophilic sequences have more charge segregation than mesophilic sequences. Moving on to the proteome level, Dr. Ghosh discussed why optimal growth temperatures are so close to cell death and whether growth rate can be quantitatively modelled as a function of temperature. Higher temperatures allow for faster reaction rates, but a little higher will denature the proteins. Lastly, Dr. Ghosh discussed proteome-folding kinetics, including minimum and maximum speed limits, and whether the folding speed can be predicted from the native protein topology. His mutation-diffusion model explains the protein folding time distribution in yeast.

Probing peptide-lipid interactions from a mechanical single-molecule perspective
Gavin King (University of Missouri)
Dr. King began his presentation with a description of what his lab does. The goal of his talk was to describe the development of a foundation for single molecule lipid-peptide

interaction assays, enabling robust interpretations. He introduces SecA – the ATPase of the general secretory system, its structure and function. He also introduces pentapeptides and the single molecule force spectroscopy method applied on the membrane. Dr. King discusses whether the method can be extended to probe peptide-lipid interactions. In order to address the major challenge of short peptides and lack of repeated domains, his approach uses a variety of geometries and peptide compositions. Dr. King described rupture force distributions for experiments with Penta-I and Penta-R and force spectroscopy analysis – position vs force, while corroborating his data with bulk measurements. Experiments with short peptides allow identification of the nature of the peptide-lipid interaction at the single amino-acid level in a near-native environment. Dr. King concludes with some future considerations on putting together measurements with modeling, which he claims may help provide a basis for improved understanding of the folding/unfolding of membrane proteins and their partitioning into the membrane.

Monomer dynamics control the first steps of aggregation and folding
Lisa Lapidus (Michigan State University)
Dr. Lapidus started her talk by describing protein aggregation from the perspective of monomer dynamics. Protein aggregation is implicated in a number of diseases, but why do proteins aggregate? She then described a model of aggregation controlled by monomer reconfiguration and has investigated the reconfiguration dynamics of unfolded proteins by measuring the rate of intramolecular diffusion, the rate one part of the chain diffuses relative to another. She measured diffusion coefficients ranging over three orders of magnitude and showed that aggregation-prone sequences tend to fall in the middle of the range. So, if you are very fast or very low, you don't tend to aggregate. Dr. Lapidus described experiments on alpha-synuclein as well as various prion sequences and correlated intramolecular diffusion of the disordered protein with solution conditions that promote aggregation. They have also begun measurements on small molecule aggregation inhibitors and found that some can prevent aggregation by shifting intramolecular diffusion out of the dangerous middle range. Finally, Dr. Lapidus used Kramers theory to address the question of how slow diffusion affects folding.

Enzymes stepping on landmines
Steve Presse (Indiana University)
Dr. Presse began by describing how enzymes are perturbed by catalytic reactions. His hypothesis states that the heat of strongly exothermic reactions perturbs enzymes. He then described the use of fluorescence correlation spectroscopy to yield diffusion coefficients and he showed that three enzymes, all catalyzing exothermic reactions, had enhanced diffusion. There are some alternate explanations for the enhanced diffusion. Dr. Presse explained how the photoacoustic spectroscopy motivates a mechanism for enhanced diffusion: the enzyme expands and retracts immediately following the catalytic reaction. Dr. Presse also addressed single molecule protein counting techniques. He discussed the limitations of conventional imaging and described both PALM (PhotoActivated Localization Microscopy) as well as threshold methods to correct for blinking. His approach uses aggregate Markov models to solve the blinking problem, which he validates using synthetic data.

Maximum Likelihood Analysis in Single-Molecule FRET
Irina Gopich (National Institutes of Health)
Dr. Gopich's talk focused on the use of single-molecule fluorescence spectroscopy in studies of macromolecular dynamics. She described the output of measurements as a sequence of photons of different colors separated by random time intervals. To improve the range of the measured dynamics at a given photon count rate, her approach considers every photon without binning. Dr. Gopich models molecular dynamics obtaining the parameters that maximize the appropriate likelihood function. She discussed the measurement of fast folding kinetics using the maximum likelihood (ML) method as well as the accuracy of the ML estimates. Dr. Gopich further discussed several aspects related to the ML analysis. This included FRET efficiency and lifetime distribution, the coupling of ML with delay times; donor delay times and the effect of acceptor blinking.

Old news and new news about single-photon absorption sensitivity in human vision
Phil Nelson (University of Pennsylvania)
Dr. Nelson started his talk with a discussion on the origins of models. He then discussed the false sense of security on the eye and to explain the importance of vision on dim light. Dr. Nelson provided a historical account of the efforts on trying to elucidate how many photons we need to be able to see. The current efforts focus on single cell experiments or experiments to obtain single cell data. He described the acceptance and rejection of photons by the first synapse with the imposition of a synapse imposed threshold. Dr. Nelson further explained how a single productive photon absorption is enough for a rod cell to signal. He continued with a discussion of the modeling challenge (transduction model vs decision module) and with a description of the Barlow model on the tightrope. He finalized his talk with a discussion on how to reconcile psychophysics with single cell experiments.

TUESDAY, FEBRUARY 9, 2016

Time Series Analysis of Diffusion with Transient Binding
John Fricks (Pennsylvania State University)
Dr. Fricks began his talk with a description of classical approaches in the biophysical literature to time series analysis of diffusion which switch between bound and unbound states. In particular, he discussed the use of hidden Markov models for the switching state space. Dr. Fricks presented a new approach that uses a stochastic expectation-maximization algorithm (EM). He discussed both the expectation (filtering) and maximization steps and described advantages on the use of hidden Markov models to the problem. Dr. Fricks described and discussed results using synthetic data. He then shifted to describe a real system – molecular motors. He described microtubule-based transport as well as classical optimal trap experiments. He also presented the paradox of codependence, or why we have two motors pushing in different directions for the same cargo. Dr. Fricks discussed three hypotheses for why that happens – the MT tethering model, the mechanical activation model and the steric disinhibition model. He concluded his talk with a discussion on the application of his method to the molecular motor movement data with different concentrations of ADP (no ATP).

Fighting antibiotic resistance by exploiting antibiotic hypersensitivity

Erdal Toprak (University of Texas)

Dr. Toprak started his talk with an historical account of the discovery of penicillin and how antibiotics work – they inhibit bacterial growth by blocking cellular pathways. He continued with a discussion on the growing public health threat of antibiotic resistance. The lack of effective antibiotic therapies against resistant pathogens has led to prolonged treatments, increased morbidity, and burgeoning health care costs. Pathogenic bacteria are increasingly resistant to antibiotics leaving clinicians with limited options for treatment. Dr. Toprak then described a novel approach (Morbidostat) to modulate the intrinsic antibiotic resistance level of bacteria and combat both the short- and long-term ineffectiveness of antibiotics. He used Morbidostat to do real time phenotyping while monitoring drug resistance using the E.coli MG1655 strain. His results show antibiotic resistance increases of 1000 fold in less than three weeks. He further described the evaluation of three drugs, all showing resistance with saturation. He used whole genome sequencing to look at mutations over time for populations under the three different drugs and found common patterns on the type of mutations occurring in the populations under the three drugs. In particular, it was found that mutations on DHFR (Dihydrofolate reductase) are responsible for resistance and that mutations are potentially acquired in a preferred order. Dr. Toprak continued with a discussion on the nature of genetic interactions that separate adaptive peaks and whether there are any dead ends. His results suggest that compatible mutations lead to a single peak while incompatible mutations lead to multiple peaks. His results also suggest that high-order epistatic interactions generate a rugged evolutionary landscape and mutations leading to resistance tend to decrease catalytic power and drug affinity.

RNA Pathways dissected at the single molecule level: The power of integrating experimental and computational approaches

Nils Walter (University of Michigan)

Dr. Walter started his talk describing his lab's work. Using the example of the RNA silencing by microRNA pathway, he made the case for why new tools are needed to interpret non-coding RNA. Dr. Walter then described the development of iSHiRLoC to detect where miRNA act. In live cells, this allows for an understanding of diffusion and the formation of molecular assembles. Dr. Walter further described the results of control experiments designed to make sure that everything is normal after injection of miRNA, i.e., to make sure that the injection does not disrupt the normal functioning of the cell. He describes the counting and the tracking of single miRNA, and showed that iSHiRLoC observations are consistent with two kinetically separated processes. He concluded this part of the talk with a description of the birth of Single Molecule Systems Biology. Dr. Walter then shifted to discuss the spliceosome molecular machinery. He described the biochemical purification process intended to isolate and probe specific spliceosomal complexes by SiMPull-FRET. His results suggest that the spliceosome is a biased Brownian ratchet machine (nanoscale thermal motion). He then proceeded to describe "bioinformatics purification: single molecule purification analysis", identifying specific spliceosomal complexes by SiMCAn. These results suggest that the SiMCAn reproduces the biased Brownian ratcheting results. He concluded his talk with a description of SiM-KARTS – a Single molecule kinetic analysis of RNA transient structure.

Information from Fluctuations: Utilizing Single-Cell Analyses to Probe Disease Mechanisms

Doug Shepherd (University of Colorado)

Dr. Shepherd began with a description of two projects where he and his group are attempting to use single-molecule and single-cell experiments for inference at large scales. In the first project the main biological consideration was small RNA regulation in bacteria. Existing data suggested that bacteria virulence was dependent on sRNA expression. The speaker developed a probe design called q-FISH in order to track small RNA without background noise and allowed resolution of specific signal. A stochastic modeling framework was used to model regulated gene expression and RNA production. Probabilistic simulations of the model were avoided by using a finite state projection method and this allowed for the determination of parameters and the testing of model archetypes. The speaker concluded with a brief explanation of the data being collected on endothelial progenitor cell heterogeneity used for the second project.

Mesoscopic modeling of DNA transport in an array of entropic barriers

Anastasios Matzavinos (Brown University)

Dr. Matzavinos began his talk with a description of the nanofluidic experiment that motivated his group's interest in tracking the motility of DNA. The data from the experiment suggested the use of a diffusion-type model in order to understand the molecular dynamics. The first aim required simulating the nanofluidics, the interaction of the fluid in the device with the DNA molecules, and also considering the molecule's behavior when diffusion has peaked. These steps were completed using the dissipative particle dynamics method, which was essential in tracking both the fluid and the molecules in the system computationally. The second aim was to develop simplified models on which mathematical analysis could be performed. The key reduction was neglecting the fluid and then a random walk formulation was used to model the motion of the DNA. Using this formalism allowed the speaker to capture the data produced in the initially described experiment.

Tracking intracellular movements

Vasileios Maroulas (University of Tennessee)

Dr. Maroulas started his talk by motivating a move away from the manual tracking of intracellular organelles and toward the use of automated algorithms. The talk focused on two techniques for tracking movements, the first relying on filtering and the latter focusing on clustering. The first technique considered organelles as evolving sets through a random set framework. The online method was able to monitor the organelles and their trajectories without assuming an a priori number. The second method views the tracking problem as a cluster paradigm and the mathematics behind this approach was a multi-object Bayes filter. Automated tracking techniques combined with a knowledge of biophysics can be used to further the study of motion within cells.

WEDNESDAY, FEBRUARY 10, 2016

A systems biology approach to characterize and rationally manipulate complex behaviors

Nitin Baliga (Institute for Systems Biology)

Dr. Baliga began with a motivation for personalized medicine and tailoring drug combinations based on the tumor characteristics of a patient. The speaker sought to reverse engineer biological networks, particularly in gliomas, through observing the effects of perturbations on a network and modeling those effects. After mining omics data from glioma patients and using the reverse engineering approach, the glioma-perturbed network predicted known therapies and drug combinations. Moreover, the network predicted a drug combination to have a synergistic effect on increasing apoptosis (or cell death) in glioma cells. This works suggests a strategy that can be followed to identify unique sets of drug targets for a network and prioritizing which combinations would work best on a given patient.

Connecting the dots across time: Gleaning signaling mechanisms from single cell snapshot data

Jayajit Das (The Ohio State University)

Dr. Das started with a review of how signal transduction in immune cells leads to a variety of cellular responses. The aim of this work was to identify single cell kinetics and protein autocorrelations from cytometry data in order to better understand signaling networks. In order to investigate this problem in the case of a linear autonomous kinetic network, bipartite matching was used to reconstruct trajectories. In the case of a nonlinear kinetic network, an approximate reconstruction was found through considerations of distributions of error rates. The speaker concluded with an example of how this process works in the case of natural killer cells.

Unraveling regulation from reaction mechanisms

John Sekar (University of Pittsburgh)

Dr. Sekar began with a brief review of autophagy and motivated the use of rule-based modeling in biology. The advantage of rule-based modeling is that it reduces the combinatorial complexity that can arise in models by using explicit descriptions of reactions. Moreover, rule-based methods can be used for microscopic considerations when background processes are important and there is a need to stearic exclusions and Michaelis-Menten mechanisms need to be explicitly encoded.

Physical limits to collective sensing by communicating cells

Andrew Mugler (Purdue University)

Dr. Mugler began his talk with an overview of modes for cellular communication. The motivating question behind this work was: Do cells sense better together than they do alone? The speaker used a coupled diffusion-type PDE model with stochastic noise terms in these considerations. Through varying the level of coupling to model direct communication, the speaker was able to produce model simulations that agreed qualitatively with experiments. The analysis of the model found that there is an optimal level of separation for cells since there is a tradeoff between the understanding of the environment gained by spreading the cells and the strength of their communication. Additionally, separation also provides no shielding and better gradient coverage.

Intrinsic Noise in Nonlinear Gene Regulation Inference

Chao Du (University of Virginia)

Dr. Du started his talk with a review of how logical and continuous systems are used to model gene regulations networks. The goal of the work presented was to develop a Markov model and inference approach that could account for the physical natures of the underlying gene regulation system. Single-cell data was used to fit many of the parameters in the multi-variate birth/death process used in the model. An important question still was the inference of parameters that could not be determined with the present data.

Inferring incompletely penetrant regulatory states in single cells

Kevin Janes (University of Virginia)

Dr. Janes focused on the problem of gaining regulatory information about single cells subject to the constraint that you cannot accurately measure cells one at a time. Incomplete penetrance occurs in a diverse group of cells where they are initially thought to be homogeneous, for example when a group of tumor cells responds to a therapy while others resist. Single cell profiling of the transcriptome through methods like q-PCR and sequencing are technically irreproducible and this issue motivated the need for a new way to acquire cellular information. The speaker sought to identify regulatory heterogeneities through a method called Stochastic profiling. The technique samples few cells, many times and looks at the average gene expression per sampling. The Stochastic profiling approach identifies genes missed by conventional profiling approaches. As an application, the speaker presented how this method can be used to study tissues from breast cancer patients and mice with carcinomas.

THURSDAY, FEBRUARY 11, 2016

Intracellular transport: The paradox of codependence among antagonistic motors

Scott McKinley (Tulane University)

Dr. McKinley talked about the bidirectionality of transport in neurons, with each movement modality carried out by molecular motors in either the kinesin (anterograde) or the dynein (retrograde) families. The current tug-of-war model describes competition and/or cooperation among motors that simultaneously bind a single vesicle to nearby microtubules that are cytoskeletal networks of thin filaments. In this context, he talked about a Tug-of-war Markov chain model proposed by Müller, Klumpp and Lipowksy in 2008 that describes the tug-of-war configuration of motors that have to attach a cargo. Recent reports also suggest that multiple identical motors help in high viscosity and motor coordination happens via tug of war mechanism. However, the current models do not account for the observation that disabling one family of motors may inhibit the performance of motors that are working in the opposite direction. Dr. McKinley discussed the paradox of codependence among antagonistic motors and a few plausible mechanisms for codependence between antagonists and the potential role of a helper protein, dynactin, in facilitating this. In addition, he showed some interesting results from their particle transport studies, e.g. the particle mean squared displacement (MSD) could be described by uniform power law, with MSD paths fitted to fractional Brownian motion (FBM); their recent finding that a Generalized Langevin Equation (GLE) model describes the particle motion better than the FBM, etc.

Maintaining homeostasis in the Drosophila midgut: a quantitative study
Nicolas Buchon (Cornell University)
Dr. Buchon's talk centered on the mechanisms that control cell dynamics in Drosophila's midgut upon microbial infection. He presented homeostasis in the fruit-fly gut, specifically how epithelium renewal is quantitatively regulated in the midgut of Drosophila, which is a highly compartmentalized organ harboring both benign and pathogenic microbes. Upon infection, both the virulence of the pathogen ingested and the immune response itself inflict damage to the gut epithelium. To maintain homeostasis, an appropriate immune response is needed to eliminate the pathogens while maintaining the beneficial microbiota followed by repair of the damage to the gut. The damage is repaired by an acceleration of epithelium renewal that combines increased delamination of enterocytes with reprogramming of intestinal stem cells to proliferate and regenerate the gut epithelium. To understand these regulatory mechanisms, one can disturb homeostasis (e.g. by infection with enteropathogens) and then study the response to the induced stress. Dr. Buchon explained how proper regulation of epithelium renewal and its coordination with immune effector mechanisms drive intestinal homeostasis and organismal health. Furthermore, experimental data were presented to show how epithelium renewal is quantitatively regulated upon infection.

Interpreting changes in cell shape: cancer invasion and metastases
Ashok Prasad (Colorado State University)
Understanding the difference in properties between non-invasive and invasive cancer cells is critical to understanding the factors that drive metastasis and one such property is cell shape. The focus of Dr. Prasad's talk was to leverage the difference in cell shapes to distinguish between samples of the less metastatic cells from the more metastatic cells. Cells from different tissues typically look quite different from each other even when cultured on plastic or glass slides under identical conditions, and it has been postulated that cell shape is a function of the cytoskeletal properties of the cells. This assumes significance in the field of cancer biology, where invasive cancer cells were shown to have altered mechanical properties compared to non-invasive cancer cells. To understand cancer invasion or metastasis, it is therefore important to assess the changes in mechanical cytoskeletal parameters that underlie the changes in cell shape. This has inspired Dr. Prasad's current research on shape characteristics of paired osteosarcoma cell lines, each consisting of a less metastatic parental line and a more metastatic line derived from the former by in vivo selection. Statistical analysis shows that shape characteristics of the metastatic cell lines are partly overlapping but on average distinguishable from the parental line. This included the principal component analysis that differentiated the invasive from the parental lines. Significantly the shape changes fall into two categories, with three paired cell lines displaying a more mesenchymal-like morphology, while the fourth displaying a change towards a more rounded morphology. In this context, Dr. Prasad discussed a neural network algorithm that can be used to distinguish between samples of the less metastatic cells from the more metastatic cells with near perfect accuracy. The next logical step in this study to is to uncover the genetic or cytoskeletal changes that underlie the subtle changes in cell shape leading to invasiveness or metastasis of osteosarcoma cancer cells. Efforts to understand how cell shape is related to cytoskeletal mechanics entail measuring cytoskeletal mechanics at the single cell level. Dr. Prasad further discussed the ongoing

experiments to infer these cellular mechanical properties by studying internal fluctuations of organelles, including mitochondrial fluctuations and calculating the mean square displacement.

Inferring neuronal synapse structure and dynamics in situ using high-resolution fluorescence imaging and analysis

Mark Bathe (Massachusetts Institute of Technology)

Dr. Bathe described the super-resolution fluorescence imaging and analysis approaches that are being developed in his laboratory to enable *in situ* mapping of (1) the translational dynamics of individual messenger RNAs that regulate synaptic protein expression; (2) the localization and copy number of individual synaptic proteins; and (3) the dynamics of amyloid aggregation within individual synapses that impact their degeneration in amyloidopathies. Neuronal synapses, the junctions between two neurons, govern signal transmission between neurons in both normal and diseased states. Synapses function as core functional units of the brain interconnecting cells to form highly intricate, spatially extended circuits that govern learning, memory, fear, and anxiety, amongst other core brain functions. Neuronal diseases including autism spectrum disorder, schizophrenia, and Alzheimer's disease are associated with genetic variations in synaptic proteins, which may impact synapse formation, stability, and signal transmission. Dr. Bathe dwelt on the importance of *in situ* characterization of synaptic protein localization, copy number, and protein-protein interactions in intact cells and tissues in understanding the underlying genetic variations that impact synaptic functions. Dr. Bathe further elaborated on the methods and approaches for integrating dynamic high-resolution fluorescence imaging with model-based computational analysis to infer super-resolved structure and dynamics of proteins and RNAs pertinent to normal brain development, as well as a range of neuronal diseases. This included an integrated Bayesian and hidden Markov model (HMM) method for annotating messenger RNA transient transport states with single step resolution. While previous HMM based methods have ignored active transport, this integrated model could capture and annotate the spatiotemporal dynamics of messenger RNAs. The live cell imaging correlates beta-actin messenger RNA, ribosomes, and focal adhesion sites in tissue culture cells. Towards the end of his talk, Dr. Bathe also briefly mentioned about new technologies for resolving multiplexed proteins in synapses, including PAINT (e.g. DNA-PAINT, Antibody-PAINT), enabling multiplexed super-resolution fluorescence imaging.

Visualizing microbial population dynamics in the larval zebrafish gut

Raghuveer Parthasarathy (University of Oregon)

Dr. Parthasarathy's talk was focused on the spatial structure and temporal dynamics of commensal microbial communities. Trillions of microbes representing hundreds of species colonize our digestive tracts, reproducing and competing with one another within local environments. The resulting ecosystems influence many aspects of the host's development and health. Although significant efforts have gone into profiling gut microbial communities, very little is known about how they vary in space and time - that is, how they grow, fluctuate, and respond to perturbations. To decipher the spatial structure and temporal dynamics of microbial communities, Dr. Parthasarathy and co-researchers have applied a light sheet fluorescence microscopy to a model system that combines a realistic /in vivo/ environment with a high degree of experimental control: larval zebrafish with

defined subsets of commensal bacterial species. First the germ-free zebrafish larvae were inoculated with fluorescently labeled *Aeromonas* and the bacterial population was quantified over time. The bacterial growth dynamics was shown to fit a logistic growth model. Interestingly, the bacterial aggregates (clustered bacteria) were observed to be growing more rapidly apparently due to higher division rates. Light sheet microscopy enabled three-dimensional imaging with high resolution over the entire intestine, providing visualizations that enabled measurement of bacterial abundances and distributions and the construction of realistic models of population dynamics. Dr. Parthasarathy elaborated on this approach and also described a recent experiment in which a colonizing bacterial species (*Aeromonas*) was challenged by the invasion of a second species (*Vibrio*). Imaging revealed dramatic population collapses driven by peristaltic activity, which differentially affects the two species due to their distinct community architectures. Further, the host genotype may determine the gut microbe competition. These findings demonstrate that stochastic perturbations and physical properties of the host environment modulate microbial population dynamics in the vertebrate gut.

Using Noise to Quantify, Predict, and Control Single-Cell Gene Regulation
Brian Munsky (Colorado State University)

Dr. Munsky's talk was on integration of single-cell experiments with precise stochastic analyses to gain new insight into gene regulation, specifically predictive understanding for Mitogen Activated Protein Kinase (MAPK) signal-activated regulation. Stochastic fluctuations can cause genetically identical cells to exhibit different behaviors even in identical environments. Often labeled "noise," these fluctuations are frequently considered a nuisance that compromises cellular responses, complicates modeling, and makes predictive understanding and control very difficult. Dr. Munsky argued that yet untapped, powerful sources of information underlies cellular fluctuations, which can be deciphered by matching fluctuations to discrete stochastic analyses. In support of this argument, Dr. Munsky explained how transcription dynamics can be experimentally quantified at high temporal (1-minute) and spatial (1-molecule) resolutions; how one can use precise computational analyses to model this data and efficiently infer biological mechanisms and parameters; and how one can predict and evaluate the extent to which model constraints (i.e., data) and uncertainty (i.e., model complexity) contribute to our overall understanding. Notably, collective responses can exhibit distinctive fluctuation fingerprints, and fluctuations may indicate gene regulation mechanisms. He then discussed how noise analysis not only helps better understand gene regulation but also introduces new opportunities to more precisely control these phenomena. Dr. Munsky talked about identification of signal–activated gene regulation, particularly utilizing stochastic analysis to understand transcriptional dynamics for the osmotic stress response pathway in yeast. A focus was to understand and quantify the expression of STL1, CTT1, and HSP12 genes that are regulated by Hog1p kinase in response to an osmotic shock. Model structures with discrete numbers of states are used to model the system, governed by stochastic transitions between states. In this framework, the observable data are the numbers of mRNAs that underlie different gene states. A finite state projection (FSP) approach determines the time-varying probability distributions. Cross-validation experiments validated four-state model to be optimal in describing the transcription dynamics.

FRIDAY, FEBRUARY 11, 2016

Bacterial colonization in fluid flow networks
Albert Siryaporn (University of California, Irvine)
Dr. Siryaporn's talk focused on how bacteria detect and respond to forces generated by fluid flow, which is common in many bacterial habitats and host organisms. Bacteria encounter a variety of mechanical forces during the course of growth and infection. Surprisingly, the bacterium *Pseudomonas aeruginosa* moves upstream, in the opposite direction of the flow. Cells attach to surfaces at the liquid-surface interface and are oriented upstream by the force of the flow. Flow reorients the cells; reversing flow reverses cell direction. Dr. Siryaporn elaborated on the mechanism of upstream migration as revealed through single-cell measurements and modeling, and discussed the consequences of this behavior at the multi-cellular level. The motility mechanism in *Pseudomonas aeruginosa* is governed by counter-advection and transverse diffusion that help disperse throughout the flow networks. Of further interest is to understand how bacteria colonize complex flow networks found in the vasculature of host organisms. How is colonization established in vasculature, and how does colonization spread in flow? Furthermore, a crucial aspect is to understand the role of bacterial mechano-sensation in virulence and colonization. Dr. Siryaporn's recent work has shown that the interplay between flow and bacterial physiology plays a critical role in determining colonization, competition between different bacterial species, and the dispersal of bacteria. These efforts and findings are critical for understanding how bacteria grow and spread during pathogenesis. Dr. Siryaporn also briefly mentioned about the ongoing work in his laboratory to identify mechano-responsive genes using RNA-Seq technology.

Dynamic fluctuations in cyclic processes
Todd Gingrich (Massachusetts Institute of Technology)
Dr. Gingrich's talk centered on dynamic fluctuations and phase transitions in cyclic processes. One of the motivating phenomena is bacterial persistence as a phenotypic switch, as was observed in *Escherichia coli* cells, a fraction of which persisted despite antibiotic treatment due to inherent heterogeneity in the bacterial population, where phenotypic switching was observed between normally cells and persister cells. Interestingly, stochastic processes that consume energy to drive dynamics around a cycle are ubiquitous in biology. Because these processes are stochastic, each realization differs. Consequently, extracted dynamical properties, like the average cycling rate, fluctuate depending on the particular trajectory that was observed. Dr. Gingrich discussed how the probability of these fluctuations can be strongly affected by subtle perturbations when there is a dynamic phase transition, and highlighted mechanisms for such a dynamic phase transition to arise using a simple toy model. Using trajectories on kinetic networks as models for driven dynamical system, Dr. Gingrich elaborated on dynamic phase transition between two distinct dynamical regimes. Towards the end, Dr. Gingrich mentioned about his recent work on a simple model system that results in dynamics allowing coexistence of two dynamical phases.

Spring Workshop 2 - Interplay of Stochastic and Deterministic Dynamics in Networks
(February 22-26, 2016)

Organizers: James Keener (University of Utah), Ruth Williams (University of California, San Diego), Lai-Sang Young (Courant Institute of Mathematical Sciences)

Reported by: Marcio Duarte Albasini Mourao, Min Wang, Xueying Wang

MONDAY, FEBRUARY 22, 2016

Stochastics in Biological Networks
Michael Reed (Duke University)
The impact of stochasticity on biological systems and its interplay with deterministic dynamics are increasingly characterized as important phenomena that need to be thoroughly investigated. The first talk of this workshop discussed main approaches to stochasticity in biological systems; that is, 1) How do systems adapt to fluctuating environments? 2) Stochastic processes can arise as an external probe of complex dynamics; 3) as a representation of underlying biological diversity; 4) as a fundamental mechanism for a biological object to achieve a specific goal. Examples such as gene regulation, homeostasis and volume transmission in the brain were presented to illustrate stochastic in biological networks. Dr. Reed emphasized at the end that one should focus on how specific biological systems work for exciting and new mathematical questions.

Regulation of Flagellar Motors in Salmonella
Jim Keener (University of Utah)
A fundamental problem that all living organisms must face is how to take measurements and make decisions based on those measurements. In this talk, Dr. Keener illustrated the use of mathematical models to examine detection and regulation of the length measurement of flagella by Salmonella. In particular, he presented mathematical models for the regulation of hook and filament length. The model for hook length regulation is based on the hypothesis that the hook length is determined by the rate of secretion of the length regulatory molecule FliK and a cleavage reaction with the gatekeeper molecule FlhB. A stochastic model for this interaction is constructed and analyzed, showing excellent agreement with hook length data. The model for filament length regulation is built based on the hypothesis that the growth of filaments is diffusion limited and is measured by negative feedback involving the regulatory protein FlgM. Thus, this model includes diffusion on a one-dimensional domain with a moving boundary, coupled with a negative feedback chemical network.

Derivation of deterministic models from stochastic models
Thomas Kurtz (University of Wisconsin)

Dr. Kurtz started his presentation with an introduction to time-change representations for Markov chains and a description of Markov change models for chemical networks. He

then explained the derivation of the law of mass action, whereby applying the law of large numbers, there is an explicit solution for the concentration of chemical species over time. Dr. Kurtz proceeded to describe the derivation of hybrid/piecewise deterministic models and averaging mechanisms used to simplify the Michaelis-Menten (MM) kinetics. In particular, assuming enzymes exist in low number, one can divide its time equation by N and take N to infinity to get an approximation for the MM kinetics. Dr. Kurtz then explained how to characterize the stationary distribution of the continuous time Markov chain. The presentation continued with a small change of gears to describe mean field approximations, exchangeability and the Finetti's theorem. Dr. Kurtz then looked at the sequence of exchangeable sequences and described the proof of the convergence of these sequences. As an example, he described results on the application of the above methodology to the neural network model by Robert and Touboul (2015), analyzing the limit and obtaining the Finetti measure.

Belief Propagation algorithms: From Matching Problems to Network Discovery in Cancer Genomics

Jennifer Chayes (Microsoft Research New England)

Dr. Chayes started her presentation with the definition of a graphical model (variables & constraints) and how to visualize dependency structures. She defined belief propagation (formulated in term of messages) and presented rigorous results on the convergence and correctness on a bipartite graph. As an example, she provided results on the maximum weight Matching problem, including a description of the algorithm for Matching. The conclusions for the Matching problem resulted in a theorem by Bayati, Borgs, Chayes and Zecchina. Dr. Chayes then shifted to present another, but more complex example: the Steiner Tree problem. Based on the problem, she introduced a new representation with the inclusion of two variables: distance and parent. In the last part of Dr. Chayes presentation, she described applications of her work to systems biology, namely in the inference of network structure from partial data; in the identification of particular nodes on the network that are responsible for particular behaviours; and in the viability of combinations of drug targets. She described her results on four case studies: the yeast protein signal transduction networks; the glioblastoma; multiple signalling pathways and; patient specific networks (Multi-PCSF) for breast cancer (TCGA breast cancer data).

TUESDAY, FEBRUARY 23, 2016

Dynamics of the visual cortex

Lai-Sang Young (New York University)

In this talk, Dr. Young discussed ongoing work in which her collaborators and she seek to model the visual cortex as a large and complex dynamical system. She started by introducing the primary visual cortex (V1) with its functions and main features, which can be structured and accomplished by interaction of large number of neurons. Dr. Young then described the realistic computational model called leaky integrate-and-fire model which explains the electrical properties of V1. A local population, which consists of two neuron subpopulations --- excitatory and inhibitory populations, with dynamics driven by competition, is also presented to illustrate the persistence of emergent clustering phenomenon. Dr. Young continued to report her research on a specific piece of modeling

work, that is, feed-forward versus recurrent input currents to neurons in cortex. The results show that cortex activity dominates feed-forward and each cortex cell has a handful number of input lateral geniculate nucleus (LGN) input, which suggest that orientation selectivity in her model works just fine and there is much diversity in model as in real cortex. Dr. Young also investigated the difference between simple and complex cells, and found that cells are simple or complex depend largely on the number of LGN. Finally she summarized her findings regarding her model from LGN to input layer of V1, and concluded with several interesting remarks which have shed light on some basic issues in visual neuroscience.

Systematic measures of ODE-modeled complex networks
Yao Li (University of Massachusetts)
Dr. Li started by introducing the background for need of systematic measures which characterize the complex biological networks modeled by a system of ordinary differential equations. He then briefly explained several systematic measures, including degeneracy, complexity, and robustness in bio-network. He also applied the theory of stochastic differential equations, including some information based theoretical measures that characterize the statistical dependency between modules on a network graph, to the derivation of the formula for degeneracy and complexity. Robustness is also defined according to the strength of attraction to the global attractor. Furthermore, Dr. Li considered stationary measures of a Fokker-Planck equation generated from small white noise perturbations of a dissipative system of ordinary differential equations, and presented some estimations of concentration of stationary measures of this model in the vicinity of the global attractor. Relationship between differential entropy of stationary measures and dimension of the global attractor is also given. Finally Dr. Li investigated some fundamental properties of these systematic measures, in particular the connections between degeneracy, complexity and robustness which are verified in several theorems.

Dynamics of stochastically switching networks: windows of opportunity
Igor Belykh (Georgia State University)
Dr. Belykh began his talk by discussing the motivation of modeling the dynamical networks with on-off interactions. He then gave two important examples, pulse-coupled neuronal networks and ecological metapopulations with sporadic dispersal. A general rigorous theory of stochastically switched dynamical networks is also presented and the rigorous mathematical techniques are applied to investigate the interplay between overall system dynamics and the stochastic switching process. That is, Dr. Belykh described the dynamical networks whose topology and intrinsic parameters stochastically change, on a time scale that ranges from fast to slow. When switching is fast, the stochastic network synchronizes as long as synchronization in the averaged network, becomes stable. And the switching network follows the average system where the dynamical law is given by the expectation of the stochastic variables. However, there are exceptions, especially in multistable networks where the trajectory may escape to another attractor with small probability. He derived explicit bounds for these probabilities using the Lyapunov function method and related them to the switching frequency and intrinsic parameters. Going beyond fast switching, he considered ecological networks of oscillators and revealed unexpected windows of intermediate switching frequencies in which

synchronization in the switching network becomes stable even though it is unstable in the average/fast-switching network. Finally Dr. Belykh talked about an interesting application of his work that describes how mathematics can help in developing a school of robotic fish with big mission of attracting real fish.

SIR dynamics on multilayer CM random network
Grzegorz Rempala (The Ohio State University)
Dr. Rempala began his presentation by motivating his work with the African Ebola outbreak in 2014. He described the Ebola transmission network and argued for the need to incorporate a heterogeneous contact network. Dr. Rempala then described the compartmental model of Ebola and the trajectory equation representation for the stochastic process as well its determinist approximation. He proceeded with the description of the standard SIR model - Kermack and McKendrick (1927), presenting a simple SIR outcome and comparing stochastic and deterministic approximations for the problem. Dr. Rempala proceeded with the description of the SIR epidemic on a configuration model (CM) graph - each vertice is a random variable q for the degree distribution (heterogeneous incorporation). This is a dynamic way of constructing the epidemics, allowing for a drop of connections to any individual. He then presented a simplified contact network S, I , d (drop), R - edge based process. The SIdR trajectory equation, X(t) is not Markovian - X(t) = X(0) +… + M(t), which is a zero-mean martingale (or innovation) process. Dr. Rempala described three main assumptions in the model: there is enough susceptibles at any time; the degree distribution has a second moment and; there is some kind of normalized initial conditions - there is a propensity function. His results show that the process converges (large N) to a determinist process under some conditions (large outbreak conditions - large number of individuals that are already infected). Further assuming that the degree distribution is of "Poisson type", there is a great degree of simplification that can be done in the network, whereby SSS can be written as a function of SS. Dr. Rempala analyzes the basic reproduction number and the size of the epidemic. His work presents an opportunity for analysis across scales and for multilayer model extension accounting for multiple interactions.

Switch modeling for gene expression time series data
Barbel Finkenstadt (University of Warwick)
Dr. Finkenstadt started her presentation with a description of sources of noise in chemical reactions networks: intrinsic stochasticity, extrinsic noise, and measurement noise. She then described the standard model of gene expression (DNA - mRNA (M) - protein (P)). She provided a summary of the reactions in the standard model of gene expression as well as the determinist rate of equations or ODEs for M and P. She finished the first part of her presentation with an early switch model fit for CCA1 clock gene. In the second part of the presentation, Dr. Finkenstadt presented a Multi-State switch model (add, delete, move a switch point). She described the ODE Switch model for mRNA, which you can formulate as a regression model for a given number of switch points. As an example, she used the mRNA expression of circadian clock genes, where one can get an overview where the clock gene switches on and off, and where you can find motifs to predict common transcription factors. In the third part of her presentation, Dr.

Finkenstadt explained how one could infer the mechanism or regulatory network of transcriptional regulation from multiple experiments in plants. She described the transcription regulation switch model (TRS) and provided a simulated example - finding the parents (transcription factor) for the genes - there are two parents needed for this regulatory model (out of 4 candidates). In the last part of her presentation, Dr. Finkenstadt described approximations for stochastic switch models, including ODE, Chemical Langevin equation (CLE), Linear noise approximation (LNA) and Birth death approximations (BDA). The Linear Noise approximation is quite good except with small number. Under the BDA, you have to do sampling but it is computationally inefficient.

WEDNESDAY, FEBRUARY 24, 2016

Phase transition for the threshold contact process, an "annealed approximation" of heterogeneous random Boolean networks

Shirshendu Chatterjee (City College of the City University of New York)

Dr. Chatterjee started by stating the performance of the Boolean network and system of differential equations in modeling the transcriptional process of gene regulation, which suggests the Boolean network models outperform the differential equation models. He then described the framework of Kauffmann's original random Boolean network, and introduced his model construction process for heterogeneous gene regulatory network that is an "annealed approximation" of Kauffmann's. In his model, genes are represented by the nodes of a random directed graph G_n on n vertices with specified degree distribution (in-degree distribution and joint distribution of in-degree and out-degree respectively), and the expression bias (the expected fraction of 1's in the Boolean functions) is same for all vertices. Then the dynamics among the genes on the Boolean network are approximated by a discrete-time threshold contact process with specified parameter. Furthermore Dr. Chatterjee characterized the order-chaos phase transition curve under two different conditions for the threshold contact process on G_n segregating the chaotic and ordered random Boolean networks. A simplified problem is taken as an example to illustrate his work and the intuition behind the results in his model is also provided. He also described the graphical representation of the threshold contact process and its dual process, from which the duality relation is derived and explained. Finally Dr. Chatterjee summarized his work on phase transition and concluded with some interesting and challenging open questions.

Exploiting single-cell fluctuations

Johan Paulsson (Harvard University)

Dr. Paulsson talked about the derivation of relations between properties of fluctuations that only reflect "local" interactions between a subset of components with a few steps known in detail but many important interactions not even identified in biological systems that are stochastic, complex, and sparsely characterized. In such systems, each component may respond to changes in any directly connected components, thus requiring knowledge of the whole to predict the dynamics of the parts, which can be addressed by the derived relations. Dr. Paulsson discussed mathematical approaches that exploit natural fluctuations to more reliably analyse data and to make predictions about what complex biological networks cannot do. Using basic mathematical inequalities, he then

established bounds for whole classes of systems. These bounds highlight fundamental trade-offs that show how efficient assembly processes must invariably exhibit large fluctuations in subunit levels and how eliminating fluctuations in one cellular component requires creating heterogeneity in another. He also illustrated the approaches by revisiting systematic single-cell gene expression data, and show that observed fluctuations contradict the assumptions made in most published models of stochastic gene expression, even when accounting for the possibility of systematic experimental artefacts. Finally Dr. Paulsson discussed some of his recent experimental results as examples on the role of fluctuations in cells, for instance, in the segregation of mitochondria, oscillations of synthetic genetic networks, bacterial cell fate decisions, and DNA repair.

Stochastic Reaction Networks with Absolute Concentration Robustness
German Enciso (University of California Irvine)

Biochemical reaction networks are highly robust regardless the total protein concentration under certain structural conditions. In this talk, Dr. Enciso presented qualitative behavior of stochastic systems for these networks. One result showed that the stochastic models admit no stationary distribution with mass near the equilibrium of the deterministic models, which demonstrates that stochastic dynamics have fundamentally different long-time behavior as compared to the corresponding deterministic dynamics. Moreover, if the time to extinction is larger than the time-scales of the system, the process will settle down to a quasi-stationary distribution before the inevitable extinction. At the end, mathematical and computational evidence are provided for demonstrating the robust behaviors of chemical reaction networks.

The Structure and Mechanisms of State Dependent Neural Correlations
Kresimir Josic (University of Houston)
Neural correlation measured in simultaneous recordings from large neural populations characterizes important aspects of neural network organization and function. However, estimating and interpreting large correlation is challenging. Moreover, the underlying mechanisms that modulate these changes are poorly understood. Dr. Josic discussed how correlation estimation can be improved by regulation. This approach was illustrated by analyzing the activity of cells in mouse visual cortex. In the second part of the talk, Dr. Josic presented a number of factors, from changes in arousal and attentional state to learning and task engagement, which modulate correlation activity. Particularly, he reviewed recent theoretical results that identify the following biophysical mechanisms of modulating spike train correlations: changes in input correlations, internal fluctuations and transfer function of single neurons.

First-passage Time to Clear the Way for Receptor-ligand Binding in a Crowed Environment
Jay Newby (University of North Carolina)
Dr. Newby presented theoretical support for an hypothesis about cell-to-cell contact, which plays an important role in immune function. A fundamental question for all cell-to-cell interfaces is how receptors and ligands contact each other, although large molecules, the extracellular fluid, and other structures in the glycocalyx separate them. This indeed

is an essential step in immunological information processing and decision-making. This talk presented a theoretical support for this hypothesis. In particular, a first passage time problem allows us to gauge whether a reaction zone can be cleared of large molecules through passive diffusion on biological relevant timescales. A complete picture of the first passage time problems is obtained by combining asymptotical and numerical approaches. The result indicates that the passive diffusion alone cannot account for experimentally observed cell-to-cell contact formation time. Therefore, cell-to-cell contact may involve unknown active mechanical processes.

THURSDAY, FEBRUARY 25, 2016

Noise and collective activity patterns of neuronal networks
Jonathan Touboul (Collège de France)
Dr. Touboul began by stating the importance of variability and noise in driving the neuronal network models from some recent literature papers. He then presented some thoughts and mathematical developments on simple models of large-scale stochastic networks, in order to uncover the complex interplay between stochastic and nonlinear dynamics under different regimes. That is, using a probabilistic approach, he addresses the question of behavior of neurons in the network as its size tends to infinity. In that limit, he showed that all neurons behaved independently and satisfied a mean field equation whose solutions are Gaussian processes such that their mean and variance satisfy a closed set of nonlinear dynamics. Furthermore, Dr. Touboul showed that network structure, as well as increased noise levels, interact with nonlinear neurons activity to induce synchronization in large-scale systems, a phenomenon already reported in the biological literature on epilepsy. He also explained that disorder can induce synchronization oscillations and his techniques only work in the presence of noise. Different genetic models of morphogenesis and more general models of competitive systems are provided as examples to help demonstrate the basic mechanism on how cortical areas develop. Finally Dr. Touboul showed that the data analysis methods for avalanche do not univocally reveal the presence of criticality: power-law scalings in local field potentials (LFPs) avalanches may only be due to the noise in the LFP recordings, and power-laws in spiking data to Boltzmann's molecular chaos, a universal phenomenon in statistical systems.

Network Cascade Models for Neuronal Synchronization
Peter Kramer (Rensselaer Polytechnic Institute)
Dr. Kramer mainly talked about his study on the synchronization of a stochastically driven, current-based, integrate-and-fire neuronal model on a preferential-attachment network with scale-free characteristics and high clustering. He started by describing the motivation and goals to build network cascade models for neuronal synchronization. The synchrony is induced by cascading total firing events where every neuron in the network fires at the same instant of time. Dr. Kramer then accurately predicted the probability that a particular statistical network model will sustain the idealized synchronous firing pattern by employing both mean-field and tree-like approximations. He also went beyond these two approximations, and conducted a detailed second-order calculation taking into

account local clustering. That is, some adaptations to the widely used analytical approximations, which are indicated for the neuroscience application, are described. His explicit analytical results are shown to give excellent agreement with direct numerical simulations for the particular preferential-attachment network model investigated. Finally Dr. Kramer explained how Watts model are mapped from integrate-and-fire model, and concluded that tree-like theories for Watts model may be workable for a network cascade.

Simplified Representation of Populations on Graphs via the Stochastic Shielding Heuristic

Peter Thomas (Case Western Reserve University)

Dr. Thomas began by reporting a novel stochastic shielding approximation (SSA) which is introduced by Schmandt and Galan as a fast, accurate simplification of randomly gated ion channel models. Viewing the channel as a discrete process on a directed graph, driven by an independent noise source for each edge, the SSA accurately represents the process using independent noise sources for only a small subset of the edges. Dr. Thomas took the Hodgkin-Huxley sodium channel model as an example to illustrate that the SSA provides accurate and efficient simulation of a population process on a graph by eliminating independent noise sources that to not make a direct contribution to the observed variance. Furthermore, Dr. Thomas and his collaborator considered the problem of finding the optimal complexity-reducing mapping from a stochastic process on a graph to an approximate process on a smaller sample space, as determined by the choice of a particular linear measurement functional on the graph. They showed the variance of the channel conductance decomposes into a sum of contributions from each directed edge, providing a metric for ranking the relative importance of each edge. Moreover Dr. Thomas discussed that the stochastic shielding heuristics remain effective for some systems with multiple time scales (ER network, 3-chain motifs), and for busty ion channel systems (nicotinic Acetylcholine receptor, IP3 channel) the original heuristic can break down, but the "edge importance" measure remains useful. Finally Dr. Thomas concluded that the stochastic shielding heuristic not only involves the evolution of conditional expectations that obey nonlinear moment equations but also provides an analytically tractable example of incorporating fluctuations "beyond the mean field" in a manner relevant to the network's physiological function.

Model reduction in stochastic bimolecular systems: tradeoffs between determinist and stochastic performance

Domitilla Del Vecchio (Massachusetts Institute of Technology)

Dr. Del Vecchio started her presentation with a description of modularity as a system's performance metric on biological systems - modularity guarantees that the input/output behavior of a system does not depend on the context (surrounding systems). She then described loading effects in a transcriptional module where she compared an isolated and a connected transcriptional component. Her lab tested the predictions with experiments in yeast and corroborated the existence of a delay (a phase shift) in the response of the connected system. She described the quantification of retroactivity using standard singular perturbation - retroactivity slows down the response of the system (accuracy degrades). However, the inclusion of noise in the model leads to a different conclusion. Dr. Del Vecchio then described existing approaches for model reduction of multi-scale

biochemical systems. She focused on multi-scale SDEs - singular perturbation techniques. Main results show that the slow subsystem filters out the noise from the fast subsystem, which she demonstrated using an academic example. Dr. Del Vecchio then proceeded by quantifying tradeoffs between signal accuracy and noise, quantifying mathematically the tradeoffs between retroactivity and noise. The analysis of noise versus the retroactivity error shows that decreasing the noise on the output will lead to the decrease in accuracy of the signal - the higher copy for "the measuring device" the less noise but also the less accuracy in the signal transmitted. Dr. Del Vecchio results suggest that natural systems constantly optimize parameters to satisfy opposing requirements. Some architectures can also break tradeoffs between noise and signal: fast load drivers between slow flanking modules reject retroactivity ensuring signal accuracy and shift noise to high frequency, so that the slower downstream systems filter it out.

When do Michaelis-Menten or Hill type propensity functions lead to accurate stochastic simulations?

Jae Kyoung Kim (Korea Advanced Institute of Science and Technology (KAIST))

Dr. Kim started his presentation with an explanation of the differences between fast and slow species in equilibrating to the quasi-steady state (QSS): fast species quickly equilibrates to quasi-steady state (QSS) while slow species changes little. He then provided a description of the Michaelis-Menten (MM) kinetics, ODEs for the MM system, and how to obtain the reduced deterministic QSSA. To deal with the stochastic system, he uses the Gillespie algorithm to change both the full and reduced systems. Dr. Kim main question is: in which conditions the full and the reduced systems are comparable using stochastic processes? In other words, in which conditions is the stochastic QSSA accurate? Dr. Kim shows that the stochastic QSSA is accurate if the derivative of the Michaelis-Menten equation, the sensitivity is small. In explaining why the sensitivity of the MM function matters, he demonstrates discrepancies between the accuracy of the deterministic QSSA and the stochastic QSSA. Dr. Kim uses two examples to show why his criteria explain the inaccuracy of the stochastic QSSA in previous systems. He finished his presentation by proposing a simple algorithm to test the accuracy of the stochastic QSSA.

FRIDAY, FEBRUARY 26, 2016

Modeling intra-host adaptation of hepatitis C-Virus

Leonid Bunimovich (Georgia Tech)

Dr. Bunimovich started his talk with an introduction to the hepatitis C virus (HCV). The hepatitis C virus is a RNA virus and infects 2.2% of the population causing liver infection, a leading cause for cancer. The virus also has a very high mutation rate. Importantly, old models overlooked the existence of a network of the virus in any single host. To overcome this issue, Dr. Bunimovich represents his network using nodes are different virus and edges as point mutations. He shows that the HCV exists in the infected host as a large heterogeneous population of intra-host variants (quasi species) evolving in the sequence space. Dr. Bunimovich also introduces the quasi-species theory, describing the frequency of variants over time dVi(t): variants differ in virulence, escape immune

response - who survives is not the fittest but the ones that are better connected. Dr. Bunimovich then describes the conventional view of the HCV (content immune escape of "arms race" between virus and immune system) and the immune system to conclude that everything is more complicated. In fact, the description of facts that do not agree with constant immune escape - high level of intra-host adaptation, complex dynamics of subpopulations, antigenic convergence. Dr. Bunimovich described two mathematical models for the HIV. He showed that antigenic cooperation (AC) explains intra-host adaptation of HCV; indirect interactions in cross immunoreactivity network and AC explain complex dynamics of HCV intra-host populations and that interference with AC is a potential strategy for prevention of chronic HCV infection.

Control of Epidemics on Complex Networks: Effectiveness of Delayed Isolation
Tiago Pereira (Imperial College London)
This presentation discussed isolation as a means to control epidemic outbreaks in complex networks, focusing on the consequences of delays in isolating infected nodes. The analysis uncovers a tipping point: when infected nodes are isolated before a critical day, the disease can be effectively controlled regardless the number of infected nodes climbs steeply for longer delays. It turns out that this critical day can be estimated explicitly in terms of network properties and disease parameters. This work can be carried out in a general framework, and it has the potential to offer insight and suggest strategies for containing outbreaks of a range of serious infectious diseases.

Diffusion in a Randomly Switching Environment
Sean Lawley (University of Utah)
Motivated by diverse applications into biochemistry and physiology, several recent models impose randomly switching boundary conditions on either a partial differential equation (PDE) or stochastic differential equation (SDE). Particularly, the PDE (resp. SDE) models arise from considering a density of particles (resp. finitely many particles) diffusing in a random environment. This presentation illustrates the use of mathematical tools to analyze these systems. The findings highlight the interesting behavior that these systems can exhibit by establishing mathematical connections between these classes of stochastic processes.

Spring Workshop 3 - Generalized Network Structures and Dynamics (March 21-25, 2016)

Organizers: Vittoria Colizza (Universite Pierre et Marie Curie), Stephen Coombes (University of Nottingham), Nina Fefferman (University of Tennessee), and Mason Porter (University of Oxford)

Reported by: Richard Buckalew, Casian Pantea, and Leili Shahriyari

Monday, March 21

Communities in Multilayer Networks
Peter Mucha (UNC Chapel Hill)

The goal of Dr. Mucha's talk was to introduce and motivate the topics of multilayer networks and community detection, and to provide some examples of these problems. His talk was organized into 4 sections: Communities, Multilayer Modularity, Multilayer Stochastic Block Models, and Detectability. Dr. Mucha began by motivating the concept of communities by showing the Zachary Karate Club example. He then demonstrated how Facebook data showing residential house affiliation at Caltech could be analyzed and clustered to reveal hidden information; students who did not report their affiliation could nonetheless be predicted based on their associations. Dr. Mucha used the opportunity to motivate the idea of communities as a description of the "high level structure" of a network. Dr. Mucha then presented data on Congressional Networks, showing polarization in two separate congresses. Dr. Mucha defined modularity for multilayer networks by generalizing the network definition, and the concept of multilayer networks was motivated by treating each two-year Congress as a layer and extending the communities in time as well as voting space. He then made an analogy to *E coli* and showed that clustering can lead to agreement on many traits, including host sex preference and drug resistance. He also mentioned applications to neuroscience and international politics. A multilayer stochastic block model (SBM) consists of a collection of probability or adjacency matrices representing layers of a multilayer network. Dr. Mucha explained how layers and nodes could be simultaneously classified into communities. The algorithm is iterative; approaches that work sequentially on layers tend to miss important connections between layers. He then showed an application of this method where he classified microorganisms according to species and location on the body. Detectability is a measure of how easily a given network can be classified into communities. It is determined by an isolated critical eigenvalue whose eigenvector encodes the community structure. As the gap shrinks, detectability decreases. As layers are added, detectability scales like the square root of the product of the number of nodes and the number of layers. Dr. Mucha then demonstrated that thresholding on the probability matrices can be almost as accurate as summing the layers. Dr. Mucha then stressed the overall importance of having multiple methods for community detection in multilayer networks.

Modeling Sequences and Temporal Networks with Dynamic Community Structures
Tiago De Paula Peixoto (Universität Bremen, ISI Foundation)

Dr. Peixoto's talk took a probability and significance based approach toward community detection. Given the general problem of starting with a stochastic block matrix and generating a cluster structure, he warned against the danger of overfitting when maximum likelihood methods are used. One potential solution is to use a Bayesian approach and maximize the posterior probabilities. Another good measure of accuracy is to minimize the "description length" of the data; a good classification is easy to describe in some sense.

To illustrate the dangers of overfitting, Dr. Peixoto presented a random SBM. By reordering the rows and columns, he showed that the matrix could be used to support a network with two communities, then six, then a large number. Since the data was randomly generated, these reorderings did not show 'real' information, and such conclusions should be avoided.

Dr. Peixoto presented several examples of increasing dimensionality for no good reason (overfitting): the American College Football data set, where no evidence can be found for allowing overlaps between communities; A social network of physicians with three

relationship types, and a random network split randomly into layers. He then showed that minimizing description length selects against these interpretations, and selects for a multilayered interpretation of data from the Brazilian Congress. Some problems with the layered approach given by Dr. Peixoto include binning (selecting time points for layers) and an inability to use layers to predict future configurations. To avoid these problems, he made an analogy to Markov Chains of arbitrary order, where a chain can be interpreted as a network with arrows from precedents (n-sequences) to tokens ($n+1^{\text{st}}$ states). By performing clustering on the resulting network, Dr. Peixoto obtained a predictive network structure that is dynamic in time. Similar techniques can be used on pure network data.
Lastly, Dr. Peixoto described a hierarchy of SBMs, as the parameters for a given SBM themselves form an SBM. In this way, one can obtain more information about a given network. He illustrated this technique using flight itineraries for several major US air carriers.

Phase Shift Synchrony and Symmetry
Marty Golubitsky (MBI and Ohio State University)
Dr. Golubitsky's talk focused on coupled systems of differential equations (DEs). He showed how the structure of the RHS of such DEs corresponds to a natural directed graph illustrating the coupling between variables in the system. Flow-invariant subspaces, not necessarily related to symmetries of the graph, can be deduced. The rest of the talk was organized into three topics: Rigid patterns of synchrony, Rigid patterns of phase-shift synchrony, and Codimension one synchrony breaking bifurcations. Rigid patterns of synchrony are patterns that do not affect the 'coloring' of nodes when a system is perturbed (nodes are similarly colored when their initial values are equal). Dr. Golubitsky described a lattice based nearest-neighbor coupled system to illustrate the idea. The rows can be colored alternately to produce a flow-invariant subspace. Then any diagonal can have its complementary coloring, which does not change the 'balanced' property of the coloring. In this way, a pattern with an arbitrary row can always be constructed; the number of such rows is the continuum, so there are uncountably many flow-invariant subspaces of such a system. Dr. Golubitsky then introduced two theorems, summarized as: "Network structure transcends symmetry" and "Admissible vector fields on flow invariant subspaces lift to the full space". For rigid phase-shift synchrony, Dr. Golubitsky introduced the symmetric network with two nodes, and showed how half-phase solutions are a necessary consequence of the network symmetry. He then considered the three node symmetric network and showed that three types of solutions exist by virtue of the network symmetry $S_6 = S_3 \times S_2$. A symmetry σ in the set of network symmetries is the product of disjoint cycles, and the order of these cycles determines the frequency of the periodic solutions, resulting in polyrhythmic solutions. Dr. Golubitsky presented the theorem: in a transitive network, rigid phase shift synchrony occurs if and only if the phase shift is forced by the symmetry of the quotient network (induced by coloring the network). He then outlined the difficult proof and invited the audience to provide a simpler one. Lastly, Dr. Golubitsky described codimension one bifurcations in the context of symmetry. Steady state such bifurcations exist for each absolutely irreducible representation of the symmetry, and Hopf bifurcations exist for each irreducible subspace. The result is that the nonlinear dynamics are determined by the type of linear dynamics present.

Computational Modeling to Contain the Spread of Influenza
Achla Marathe (Virginia Tech University)
Dr. Marathe uses agent-based modeling approaches to design strategies for the control of the spread of influenza. Her techniques include relational and network based interventions, models that are dynamic in time and health states, and realistic social networks. The model that Dr. Marathe presented includes two types of intervention: bottom-up (private) interventions, where an individual well immunize or treat oneself as their social contacts fall ill, and top-down (public), where either a census block or a school is immunized or treated in response to an outbreak in the community. The model consists of a large number of SEIR within-host models coupled along a realistic, interaction based network intended to mimic the characteristics of Miami, Florida. The factorial design of Dr. Marathe's study required 4000 simulation runs to study the effect of varying diagnosis rates, viral infectivity, treatment type and delay, and other factors. Her results demonstrated that block level vaccinations are by far the most effective intervention, effectively walling off an epidemic before it can spread widely. When resources are scarce, a school-level vaccination program may be the best option. She also noted that compliance levels were of minor importance, and the delay before treatment was relatively unimportant as well. Dr. Marathe's overall message was: in public health, the fewer resources one has, the more valuable local information becomes.

Emergent Physics of Processes Interacting on Multiplex Network Structures
Alex Arenas (Universitat Rovira I Virgili)
Dr. Arenas presented a multilayer model of brain activity consisting of blood flow (energy transport) and brain activity (neuronal connectivity) layers. Nodes represent neurons, and different connectivity types are represented on each layer. Dr. Arenas stressed the difference between multilayer and multiplex networks – in the latter, all layers contain the same nodes, including identity connections between the layers. In this setting, an adjacency tensor plays an analogous role to the adjacency matrix in a single-layer model. For the model Dr. Arenas presented, neural activity was represented by a system of Kuramoto oscillators whose internal dynamics are governed by the availability of energy. Blood flow was represented by a biased random walk, where the bias points in the direction of high activity, representing high energy need. The model shows phase transitions between disorder and synchrony, as the bias and coupling strength are increased. When the bias is high, there is a bistable region where both synchrony and disorder are stable solutions, which Dr. Arenas conjectured to represent the phenomenon of sudden switching from rest to cognition in neurons. Dr. Arenas then showed that his model was effective at discriminating schizophrenic patients from MRI data sets, and more effective than models with only a single layer.

Tuesday, March 22, 2016

Operads as a potential foundation for systems of systems
David Spivak (MIT)
Using elements of category theory, a mathematical theory of operads is proposed as a foundation for studying systems (viewed here roughly as an assemblage of subsystems

whose local interactions give rise to the global behavior). Systems can be classified in terms of their composition styles (e.g. feed-forward, feedback, port graphs), with structural features (interfacing, composition, nesting) differentiating between them. Different types of operads may be required for different types of systems, but they are linked by "composition mappings". For example, a system with dynamic network topology can be mapped into a system with static network topology by fixing a time point. Open dynamical systems (ODEs or boolean) are cases of systems of particular interest. They can be interconnected to form large-scale systems, and thus fall under the scope of the proposed theory. It is generally a difficult task to infer dynamical properties of the large scale network from behaviors of its components, but it is shown here that steady state matrices of boolean systems can be computed from steady state matrices of component systems using standard matrix operations.

Synchronization of coupled systems: Relating network structure to dynamics
Georgi Medvedev (Drexel)
Many applications (from neural networks to power grids) lend themselves to a local to global approach to the study of their dynamics; the common setting is a set of dynamical systems, viewed as nodes of a graph, and coupled along its edges. How do dynamical properties of the nodes translate into behaviors of the overall system? Here the presenter focuses on synchronization. Connectivity (and in particular algebraic connectivity, i.e. the second smallest eigenvalue of the graph Laplacian matrix) plays a key role in the analysis. It turns out that families of graphs on n vertices with bounded algebraic connectivity (as n grows) are particularly well-suited for synchronization. These fall roughly under the class of spectral expanders graphs. Two representative models were chosen to illustrate synchronization on graphs. In the first one each node is a map with chaotic behavior. In this case a technical sufficient condition for synchronization is given in terms of algebraic connectivity and spectral radius of the graph Laplacian. It is found that connectivity plays a very important role here: complete, Erdos-Renyi random graphs, and pseudo-random graphs favor synchronization, while finite-degree Cayley graphs do not. The second model is a conductance-based model of LC neurons. Here it turns out that under weak electrical coupling only rough features of the connectivity (e.g. number of edges) play a role, while for strong coupling the finer properties of connectivity (algebraic connectivity, cycle structure) become important. In the latter case, network activity is slowed down and synchronization is favored.

Exponential random simplicial complexes
Dmitri Krioukov (Northeastern)
Interactions involving more than two components are widespread among real networks (e.g. collaboration networks), including biology (e.g. protein interactions, gene regulation, etc.). While graphs completely capture dyadic interactions, higher-dimensional simplicial complexes are used to model n-party (n>2) interactions. This talk discusses the class of exponential random simplicial complexes (ERSCs) that generalize exponential random graphs (ERGs). ERGs are random graph ensembles where the observables (edges of the graph) follow independent Bernoulli distributions with means constrained to specific values. ERGs provide a conceptual framework for statistical modeling of network data and are well-studied descriptive models, used in real network settings to model structure,

predict dynamics, optimize function, etc. In the class of random simplicial complexes introduced here, simplices of a certain dimension are independent Bernoulli random variables, and their expected number is constrained to a fixed value. A second type of constraint fixes the expected number of boundaries. It is shown that aside from these two types of constraints, the exponential random simplicial complexes are ``canonical", i.e. they are unbiased with respect to other structural properties. The class of ERSCs is shown to subsume standard simplicial structures used in applications, e.g. Erdos-Renyi random graphs, random flag complexes, and Linian-Meshulam random complexes.

Generalized network structures: simplicial complexes
Ginestra Bianconi (Queen Mary)
Interactions between more than two nodes can be encoded via simplicial complexes: applications range from neural networks and social networks to quantum gravity, where the geometrical features of simplicial complexes are particularly important. In fact, simplicial complexes are particularly well suited for models of networks where geometry of the network emerges spontaneously from its dynamics. This talk presents a new model of evolving simplicial complexes, called NGF (network geometry with flavor). The underlying intuition is that complex networks have an inherent hidden metric, and therefore, by the triangle inequality, if a node connects to two nodes, then the latter two must be close to each other. NGF limits the number of triangles that a link can be a part of, and proceeds in two steps: first, a triangle with one new node and two new links is added along a link that has not reached its maximum number of triangles; and second, two nodes at distance two are linked with a certain probability. It turns out that NGF can generate networks with a wide range of geometries, from chains to scale-free networks with small-world properties. It is shown that the rules described above generate an efficient preferential attachment mechanism, without the need of specifying one a priori, and thus scale-free topologies arise naturally.

Topological Data Analysis for investigation of Dynamics and Networks
Heather Harrington (University of Oxford)
Dr. Harrington is interested in temporal networks, where edges may appear or disappear over time. She presented models of such networks via subgraph sequences generated by time stamps for each edge, determining at which time steps the edge is present. In the case of additive edges only, this procedure produces a sequence of graphs ordered by inclusion. By adding a simplicial structure to each graph, this model produces a complex similar to the Rips complex in computational homology. In an analogous manner, Dr. Harrington can then generate a temporal bar graph showing which network features persist over time. Dr. Harrington also presented a method whereby a weighted graph can be used to create a similar complex, by including edges in order of their weights. In the more interesting case where edges can be added and deleted, Dr. Harrington applied the concept of "Zigzag Persistence" whereby graphs are mapped through their union, to produce an ordered sequence of subgraphs, as before. She then noted that different types of time stamps on edges produce qualitatively different zigzag barcodes. Dr. Harrington's next goal is to use similarity measures to detect the underlying time stamps based on barcode data, and found that both the bottleneck distance and the landscape distance were mostly effective, but could not discriminate between the "bursting" and "periodic" type time stamps. She solved

this problem by defining a "Topological Profile" of detrended data, which then reflected the periodicity of the periodic model. Dr. Harrington closed by noting that zigzag persistence is computationally very expensive, and currently is not feasible for realistic data sets. She also noted that these methods may also be useful for neuroscience.

Temporal Networks Supporting Cognition in the Human brain
Danielle Bassett (University of Pennsylvania)
Dr. Bassett began with an overview of the brain as a network. She then defined the concept of network efficiency with the hypothesis that more efficient brains are somehow "better". In fact, using advanced brain mapping techniques, she showed that brains with more network efficiency corresponded to higher IQ scores. Dr. Bassett distinguished between the "highway" and the "traffic" – although connections exist, information may not always be flowing on all possible paths. She thus demonstrated that fMRI techniques could be used to map the "traffic" by drawing edges between brain regions whose activity are correlated. Dr. Bassett then applied these techniques to study learning in a Guitar Hero style challenge; she quantified learning by fitting a decaying exponential to the task completion time. She then used the concept of multilayer modularity to define a concept called flexibility, which is a measure of how willing individual nodes are to switch their allegiance to communities. She found that individuals whose brains showed higher flexibility also showed faster learning. In an attempt to tease out the cause of flexibility, Dr. Bassett drew connections to mood and to the drug DXM, suggesting that multiple neurotransmitters likely play a role in flexibility. She also showed that flexibility varies across brain regions; in particular the visual and motor cortices have very low flexibility. Connectivity between these regions decreases during learning, demonstrating with data the experiential effect of "muscle memory".

Brain Control
Jeff Moehlis (UC Santa Barbara)
Dr. Moehlis studies Parkinson's disease with the hypothesis that it is caused by unwanted synchronization between motor neurons. His goal is to use optimal control techniques to optimize deep brain stimulation (DBS) to desynchronize those neurons. DBS uses high frequency pulsatile inputs at approximately 100 Hz, and is always active. There are "Arnold Tongue" regions in frequency – amplitude space corresponding to different clustering patterns induced by DBS, and the hypothesis is that DBS works by dispersing the otherwise synchronized neural oscillators it affects. DBS uses a pacemaker with a batter, and the battery must be surgically implanted and last only a couple of years. In order to reduce the surgical burden on patients, Dr. Moehlis has the goal of optimizing power usage for DBS. To this end, he uses a model of phase coupled oscillators, and acts to maximize the Lyapunov exponent present in the "phase difference variable" using the calculus of variations. An optimal control input is deduced. This input is only applied when the mean field potential is above a certain threshold (indicating synchrony). The result is a 1000-fold decrease in power consumption while maintaining desynchronization. Another method Dr. Moehlis described uses the concept of isochrons, curves in phase space corresponding to phase-synchronized initial conditions. Near the fixed point of a coupled oscillator model, the isochrons are tightly packed. The control scheme here is to push the state variables toward this region, where they all end up on different isochrons and thus become

desynchronized. This method is extremely effective, but has higher power requirements than the first.

Wednesday, March 23, 2016

Statistical methods for modeling network distributions
Jennifer Neville (Purdue University)
Dr. Neville classified large class of networks that we have as edge based statistical models of networks structure. She highlighted that the efficient sampling and inference algorithms are crucial for tractable analysis in large-scale domains evolving over time. Then, she explained Kronecker product graph model (KPGM), and emphasized that the space of graphs exhibits a combinatorial structure that poses challenges to accurate estimation and efficient sampling/inference. The speaker described her group-sampling algorithm, which is linear time order O(E), where E is the number of edges. She also spoke about her developed mixed KPGMs, which generates the first l levels using the original KPGM. Dr. Neville also explained about how to generate attributed networks. At the end, the speaker talked about her current work, which extends the AGM framework for hierarchical latent variable graph models (e.g., mKPGMs, BETR), and corresponds to sampling from a graphical model with context-specific dependence, requires more complex inference.

Contagion maps for examining spreading processes on networks
Dane Taylor (University of North Carolina, Chapel Hill)
Dr. Taylor started by talking about epidemics on modern network, and contagions on spatially embedded networks. He also talked about social contagions on modern networks, and the amount of social reinforcement required for someone to adopt contagion influences "how" it spreads. Then he described the Watts threshold models (WTM) for social contagions. The speaker also explained several noisy geometric networks and embedding networks in metric spaces. Moreover, he described the manifold learning with contagion maps; studying WTM maps using a combination of two mathematical fields; topological data analysis and nonlinear dimension reduction. He created "contagion maps" that use multiple contagions on a network to map the nodes as a point cloud. He applied the developed model on noisy ring lattices.

Assessing the vulnerability to infections of time-evolving contact networks
Chiara Poletto (Universit'e de Paris)
Dr. Poletto started by presenting an example for disease spread; western Africa Ebola outbreak 2014-2015. She then explains our understanding of communicable disease prevention and control is rooted in the theory of host population transmission dynamics, and the disease's spread depends on network of host-to-host contacts as well as the transmission's occurrences. She emphasized on the importance of the contact network for spreading the disease by presenting the HIV's spread graph.
She offered a new approach for identifying the temporal aspects of the contact patterns that are critical for disease transmission. The speaker focused on risk assessment analyses based on the identification of the epidemic threshold. Therefore, Dr. Poletto developed a theoretical infection propagator model, which relays on the knowledge of the sequence of adjacency matrices describing the temporal network. The speaker also discussed the

mathematical formulation of the developed method for various disease compartmental schemes, SIS, SIR, SIRS and SEIS models. She also presented some examples of how this model can be used to obtain insights on the factors driving the epidemic risk.

Predictive Integration of Networked Big Data: From Biology to Economics
Nataša Pržulj (Imperial College London)
Dr. Przulj started her talk by explaining why we need the heuristic algorithms. She developed a model using graphlets as logos of networks, and extracted information from one network. She applied the model on word trade network 1962-2013. She also talked about network alignment and network data integration. She described a method to reconstruct gene ontology. She used the same method for ovarian cancer patient's data set to classify the patients. Moreover, she introduced a adaptable data fusion framework that can effectively integrate somatic mutation data, molecular interactions and drug chemical data to address three key challenges in cancer research: stratification of patients into groups having different clinical outcomes, prediction of driver genes whose mutations trigger the onset and development of cancers, and re-purposing of drugs for treating particular cancer patient groups. This new methods stem from network science approaches coupled with graph-regularized non-negative matrix tri-factorization, a machine learning technique for co-clustering heterogeneous datasets.

Promiscuity in Multilayer Networks
Florian Klimm (University of Oxford)
The speaker started his talk by mentioning that in protein interaction network some interactions are stronger and some are more stable than others. Nodes are often not equally important in each layer but also layers are not equally important. Promiscuity varies widely across networks. He mentioned that airports are also hierarchically organized and some airports have more connections than others.

Hierarchical Networks
Sophie Rayner (University of Aberdeen)
She explained the Hierarchal or multi-scale graphs, and two different ways that one can present these graphs. She mentioned looking at systems from multiple points of view increase our toolbox for understanding them. At the end, the speaker asked for the help to apply her approach on some data sets.

Non-parametric distributed algorithms for network based anomaly detection
Natalie Lemanski (Rutgers University at New Brunswick)
The speaker started her talk by mentioning the inspiration of this project, which was the security for the computer's networks. It would be beneficial if the nodes share information about the attacks. You need to detect attacks quickly and react quickly. Natural systems under similar constrains are honeybees do this well to find food. She said from these networks we get non-parametric distributed anomaly detection and migration.

Half baked idea: How to spot the nodes that make a temporal network vulnerable
Eugenio Valdano (Pierre Louis Institute of Epidemiology and Public Health)

The speaker started his talk by remarking the largest eigenvalue is the critical point for the infection propagator in discrete-time temporal networks. Instead of using large eigenvalue he studied the associated eigenvector. He applied his method for f2f contact network @ conference, 1 day, 102 people, and 30s resolution. The result was that the strong nodes depend on the time scale of the epidemic.

On the mechanisms for persistence of the rabies virus (RABV): incubation period heterogeneity and effects of movement network

Davide Colombi (Institute for Scientific Interchange)

The speaker investigated the problem of RABV in Central African Republic, started with two hypotheses using metapopulation approach. He used SEIR stochastic model to consider spatial fragmentation and migration from human to canine population human to dog ratio (urban, rural). As results, he found the persistence of the virus spatial structure heterogeneity in incubation no spatial structure. He observed the crucial role of heterogeneity of incubation period.

Comparing dynamic networks in different time scales

Tanya Berger-Wolf (University of Illinois)

She asked audiences if anyone know about a method to compare dynamics networks, for example comparing genetics and social networks for the same population in different time scale. Then, she presented her idea about how to compare these two networks. She also asked if we have a good predictive of the network's structure, how much information from networks A could change the prediction from the outcome of the network B.

Bootstrap percolation on Z_m^{d1} x K_n^{d2}

David Sivakoff (The Ohio State University)

He talked about the very specific dynamics on special class of graphs or lattices. Given a graph, which is a Cartesian product of a lattice and a graph, he used bootstrap percolation. He start with random vertices and then follow an algorithm, which keeps the infected nodes infected and makes infected their neighbors at each updating time step. For example he applied the technique on the Cartesian product of two complete graphs. He also provided a brief history of bootstrap percolation.

Mutualistic networks

Carrie Eaton (Unity College)

Dr. Eaton presented some examples of ecological and bipartite networks, and the main goal that is maximizing the fitness. Where, fitness is the expected value of interaction. Then she explained the plant-pollinator mutualistic networks. At the end, the speaker highlighted the emergent network structure.

The hat problem and forbidden subgraphs

Puck Rombach (University of California, Los Angeles)

The speaker started her talk by explaining the guessing hat problem and the rules of this game. She also discussed forbidden induced sub-graphs. At the end she mentioned that she is interested to know about the application of the discussed problems in biology.

Network vector fields
Eddie Nijholt (VU Amsterdam)
He was looking at vector fields where they have a specific kind of symmetry. He then looked at network vector fields on a three nodes directed graph. Then he considered a symmetric directed graph with five nodes. He also emphasized that symmetries in general are non invertible. The speaker concluded that the problem of finding generic bifurcations in network vector fields becomes one of equivariant dynamics.

Reconstructing infectious disease transmission networks using genomic data
Rowland Kao (University of Glasgow)
Dr. Kao talked about the evolutionary and epidemiological approaches to analyzing deep sequence data in livestock and wild life. He mentioned that applying inductive inference to individual events could be frustrating. He also noted a clash of culture and difference of the thinking formed the disease's spread. We use the data in very specific way. Moreover, he presented modeling approaches to forensic phylodynamics. He also highlighted that contact tracing data are often difficult to obtain particularly where multiple host species are involved. The development of high throughput sequencing technology means that highly resolved data could now be generated to inform the identification of transmission chains. He considered the application of these data to exemplar systems, and emphasized how different approaches respectively adopt evolutionary and epidemiological perspectives to provide insight into this important problem. He mentioned the transmission Patterns for BVD: viral disease of cattle, sequence data aggregated into 14 regions. Additionally, he explained coalescent models, population size and TMRCA, and the limitation of coalescent models, as well as challenges of interpretation: multiple route of infection, mixed samples, generation of within host diversity.

Thursday, March 24, 2016

Graph Algorithms: A practical, parameterized point of view
Blair Sullivan (NC State)
In the world of network algorithms, most problems are NP-hard. To circumvent this difficulty, various ad-hoc heuristics can be used, but the results are not always reliable. However, while these general remarks are true for random networks, real world networks often have inherent structure that can be taken advantage of when designing algorithms. Various types of graph algorithms (e.g. maximal weighted independent set, minimal vertex cover, subgraph isomorphism, min.cut/max. flow, connectivity, clustering, etc) are relevant in practical applications, and their performance is measured as an asymptotic on the worst-case scenario performance; this results in "complexity" classes (e.g. P, NP, etc). It is often useful in real-world networks to work with parameter-dependent classes -- for example, FPT (fixed-parameter tractable, O(f(k)n^c)), or XP, O(n^f(k)). This is because in practice parameters k may be bounded, or limited to bounded values because of computation costs and other constraints. This approach may simplify algorithms dramatically. For example, the vertex cover algorithm (finding the minimum number of vertices that hit all edges) is NP-complete, but the k-vertex cover algorithm (deciding if there exist at most k vertices that hit all edges) is FPT: a brute-force approach yields complexity O(n^k), while a greedy rule leads to O(2^k n).

Two newly-developed algorithms relevant to biological applications were presented. They are both FPT complex, and they are also shown to have bounded expansion (a formalization of sparsity). The first algorithm refers to the minimum number of edges that must be removed to obtain (a disjoint union of) paths, with application to DNA data analysis; the second algorithm is about counting motifs, with direct applications to brain cell networks.

Multilayer networks
Mikko Kivela (Aalto University)
It is often very useful to represent real-world interactions as graphs. Many real world models have been developed this way, and much of the advancement of network science has been based on this approach. However, as data becomes more and more accessible, it becomes clear that in natural settings the interactions are much more complicated and may encompass a variety of connection types and time-dependence; moreover, the model network may be naturally the result of combining a number of interdependent, but structurally/functionally distinct, subnetworks. Examples of such structures are common among social networks (e.g. interconnected networks of Google, Twitter, Facebook accounts), transportation networks (interconnected airline, train and bus networks), city infrastructure (e.g. interconnected road/subway networks).
This talk presented a general framework for "multilayer networks", which allows the study of aforementioned situations in a unified and comprehensive fashion. The framework unifies disparate existing terminologies (multiplex networks, interdependent networks, networks of networks, etc.)

Network representations of multimodal transportation systems
Saray Shai (UNC Chapel Hill)
In recent approaches, metropolitan areas have been viewed as complex systems, encompassing a series of interconnected networks (infrastructure and transportation networks, mobility networks, proximity networks etc.) Here the focus is on multiplex networks of multimodal transportation.

An empirical study is discussed for the coupling between the street network and the subway for London and New York. Although the geometries of the two multiplex networks are different, there are similarities related to quickest paths. On the other hand, there are differences in the optimal subway speed for avoiding congestion: London admits such an optimal speed, but New York does not. It is also shown that optimizing the subway speed does not necessarily mean increasing it, as that may lead to uneven spatial distributions of accessibility.

Dynamic Interaction Networks: from Inference to Insight
Tanya Berger-Wolf (UIC)
From a practical perspective, networks can be viewed as abstract representations of underlying processes (e.g. mobility, activity, who talks to who etc) that generate raw data. Once data is collected (e.g. in social networks, via direct observation, or via (large scale) GPS tracking, etc), a series of decisions are made to arrive at a network model, from

constructing the network itself to choosing a representation (e.g. stream of edges, time series, static graph, etc.). Another way of representing networks is via multilayer networks, who have recently been extensively used in applications in social media, vaccination and disease control, marketing, networks, brain networks, etc. In dynamic networks it is customary to take static snapshots, construct time series of structural features (e.g. degree distributions), and infer pattern and structure from this information. A crucial step in this process is choosing an appropriate time scale for aggregating data in this way: if the scale is too small, then a lot of redundant information is generated, while a too long time scale results in crucial data loss. A method for Temporal Scale Inference is illustrated, and shown to produce time scales that are in agreement with those of the underlying natural processes for networks of baboons, zebras, and brain cells. The presentation also included a discussion of algorithms for predicting spatial location of an individual from the location of its neighbors. It is shown that the correct network here is not the proximity network, but rather the "leadership network"; this is a directed graph where A->B if A is likely to follow spacial trajectories of B, and is constructed from multidimensional time series data. A similar framework is shown to generate efficient clustering methods in dynamic networks, where a notion of cost (distance) is defined to penalize or reward individuals for switching communities (e.g. in terms of social status, harassment, or access to resources).

A multilayer distributed clock synchronization algorithm
Hanbaek Lyu (Ohio State)
The problem is stated in terms of identical clocks of equal frequencies on the vertices of a connected graph. The clocks can communicate only with their neighbors, and the aim to synchronize all clocks. A simpler model is when the clocks are digital; however, even in this case there are graphs where no solution exists. In this talk the distributed clock synchronization is considered on trees. It is shown that if n is 3,4,5 or 6, then the tree is n-synchronizing iff its maximal degree is strictly less than n. Possible applications of the result include wireless sensor networks, data fusion in distributed networks, and pacemakers.

Control of complex networks requires both structure and dynamics
Alexander J Gates (Indiana)
The working definition of control here is finding a subset of variables that can be intervened upon to drive the systems onto specific trajectories. The specific case of Boolean networks is considered, and it is shown that structure of the prediction based on network structure alone can both underestimate and overestimate the set of variables that can control the system. It is also shown that if one is only interested in controlling steady states, rather than full trajectories, than structure can predict controllability with a much higher probability of success.

Friday, March 25, 2016

Reconstructing connectivity of oscillatory and chaotic networks from observations
Arkady Pikovsky (University of Potsdam)
Dr. Pikovsky first explained the phase description of two coupled oscillators. He described how to start from a scalar observable to protophase and then from protophase to genuine

phase. He elucidated the network structure of oscillators and phase reduction. He also explained different types of pairwise and triple couplings. Dr. Pikovsky then presented the generalized idea about how to reconstruct phase equations and define coupling norms. Moreover, the speaker described three van der Pol oscillators, and reconstruction for both small and stronger couplings. Furthermore, Dr. Pikovsky explained partial triple coupling and its results for random network of 5 oscillators. He mentioned that reconstruction of observable-independent equations of phase dynamics provides complete description of interacting systems within the phase approximation. He also described the Ermentrout and Terman model of the neural field. The speaker concluded that knowledge on the structure of equations helps in recovering the network for the chaotic neural field network.

Inferring the connectivity of coupled dynamical units from time-series statistical similarity analysis
Cristina Masoller (Polytechnical University of Cataluña)
Dr. Massoller described the climate system and how networks are applied in this system. She also mentioned that one could use brain networks to model climate network. She used a nonlinear measure to quantify statistical interdependency. Furthermore, Dr. Masoller enlightened methods of symbolic time-series analysis to obtain patterns in the time series. Moreover, the speaker presented the methods to construct a network to predict El Nino, which is an important climate phenomenon. Dr. Masoller also illustrated the Kuramoto oscillators in a random network. She also presented her current project, which is an application of Hilbert transform for inferring the climate network. In addition, the speaker developed a network to identify regions with similar climate.

Spring Workshop 4 - Control and Observability of Network Dynamics (April 11-15, 2016)

Organizers: Reka Albert (Pennsylvania State University), John Baillieul (Boston University), Adilson Motter (Northwestern University)

Report by: Farrah Sadre-Marandi, Reginald McGee, and Ying Zhou

MONDAY, APRIL 11, 2016

Control Theory, Networks, and Life Itself -- Reprise
John Baillieul (Boston University)
In this talk, the speaker gave an overview of real-time networked control systems as an introduction of the workshop. For example, Bosch GmbH began a feasibility study of using networked devices to control different functions in passenger cars. The study bore fruit, and later the communications protocol of the Contgrol Area Network was announced at the Congress of the Society of Automotive Engineers. Driven by technological developments in embedded systems, the proliferation of MEMS device arrays, the realization that life itself is supported by biomolecular networks, interest in multiagent robotics, and many other factors, the technology of real-time networked

control systems has become perhaps the most important component of the rapidly emerging science of networks.

Subtle is the noise, but malicious it is not: exploring the benefits of intracellular noise
Mustafa Khammash (ETH-Zurich)
The speaker demonstrated how novel and beneficial functional features can emerge from exquisite interactions between intracellular noise and network dynamics using homeostasic regulation and oscillatory entrainment as examples. The speaker introduced a theoretical framework for biological regulation that combines ideas from probability and control theory and explicitly takes into account intracellular noise. Using this framework, the speaker introduced a new regulatory motif that exploits stochastic noise, using it to achieve precise regulation and perfect adaptation in scenarios where similar deterministic regulation fails. The speaker then propose a novel role of intracellular noise in the entrainment of decoupled biological oscillators, and showed that while intrinsic noise may inhibit oscillatory activity in individual oscillators, it can actually induce the entrainment of a population of such oscillators. Thus in both regulation and oscillatory entrainment, beneficial dynamic features exist not only in spite of the noise, but rather because of it.

Inference, Validation, and Control in Networked Neuronal Systems

Kimberly Schlesinger (University of California, Santa Barbara)

This talk was about the mesoscale dynamics of an interconnected culture of neurons grown atop a multi-electrode array. The work presented was from a collaboration with expertise in neuroscience, instrumentation and microscopy, and theoretical and statistical modeling, The speaker used high-resolution spiking data available from this network, as well as the precise control afforded by a novel neural circuit probe apparatus. The speaker discussed preliminary results and future efforts toward building an interactive framework for classification of network dysfunction, real-time selection of interventions for validation and control, and investigating multiscale interactions between populations.

Optimal Causation Entropy: Information-theoretic Reverse Engineering of Biological Networks

Jie Sun (Clarkson University)

The speaker introduced a computational approach to calculate the optimal causation entropy (oCSE), which is used to infer causal networks from data. The task of inferring the underlying cause-and-effect network from observational data is challenging, especially when the underlying system consists of a large number of interacting components and the dynamics is intrinsically nonlinear. The speaker was able to demonstrate the effectiveness of the causation entropy method using both synthetic and experimental data.

Network control offers a fundamental mechanism of executive function

Danielle Bassett (University of Pennsylvania)

In this talk, the speaker presented the theory that network control can be a fundamental mechanism of ``cognitive control". Cognitive control is a type of executive function of the brain that facilitates brain capabilities such as decision-making, inhibit inappropriate behaviors, or switch between different cognitive tasks. A few specific regions of the human brain drive cognitive control. The speaker demonstrated how to use structural controllability theory in the context of images of brains. Beginning with a linear model, the speaker demonstrated that the exact location of regions within the brain's structural wiring explain their roles in cognitive function. For example, the regions of ``average controllability", which are the regions that steer to many easily reachable states, are those regions that are active when the person is idling. The regions of ``modal controllability", which are the regions that steer to few difficult-to-reach states, are the regions that are active when we steer between different tasks. The regions of ``boundary controllability", which are the regions that are used when we need to connect different ideas to solve problems, are the regions that are responsible for paying attention. The speaker then discussed the potential applications of this new knowledge in the context of clinical interventions in people with neurological disease and psychiatric disorders. Finally, the speaker briefly talked about the extensions of the work, i.e. 1) with nonlinear dynamics (coupled Wilson-Cowan oscillators); 2) finite-time, finite-energy optimization problem instead of infinity time, infinite-energy optimization; 3) linking control to executive function.

Formal Verification and Synthesis of Spatial Temporal Pattern for Networked Systems

Zhaodan Kong (University of California, Davis)

In this talk, the speaker proposed a new logic called Spatial-Temporal Logic (SpaTeL) that is a unification of signal temporal logic (STL) and tree spatial superposition logic (TSSL). SpaTeL is capable of describing high-level spatial patterns that change over time. The speaker presented a statistical model checking procedure that evaluates the probability with which a networked system satisfies a SpaTeL formula. The speaker also showed a synthesis procedure that determines system parameters maximizing the average degree of satisfaction, a continuous measure that quantifies how strongly a system execution satisfies a given formula. Examples of biological system models were used to demonstrate the use of SpaTeL.

Redundancy and control in complex networks

Luis Rocha (Indiana University)

In this talk, the speaker presented two concepts that are used to control complex systems. The first concept is the schema redescription methodology, which is used to remove redundancy from automata rules to reveal their canalization properties, thus simplifying the characterization of control in large models of natural networks, such as systems biology models of biochemical regulation. The second concept is effective connectivity

and input redundancy, which is a measure of canalization. The speaker demonstrated that effective connectivity is an order parameter of Boolean Network (BN) dynamics, and a major factor in network controllability. It was also shown that existing structural control methods do not predict the actual controllability of Boolean network models, as they can both undershoot and overshoot the number and which sets of variables actually control these models, highlighting the importance of the system dynamics in determining control. Finally, it was shown that controllability can both be hindered or aided by how canalization unfolds in a given network, leaving room for natural selection or human design to effectively control large complex networks

Hidden interactions in gene networks and their mitigation through distributed feedback control
Domitilla Del Vecchio (Massachusetts Institute of Technology)
In this talk, the speaker presented a systematic modeling framework that captures hidden interactions in a network's description and provides simple graphical rules to draw them. The speaker presented recent experimental results that validate these predictions. The speaker also illustrated that a distributed control scheme, in which the local negative feedback at each node is realized through mRNA interference, can mitigate the effects of those hidden interactions due to scarcity of resources needed for gene expression.

TUESDAY, APRIL 12, 2016

Excitable and other dynamic behaviors in migrating cells
Pablo Iglesias (Johns Hopkins University)
Dr. Iglesias began his talk with an overview of motility, gradient sensing, and polarization; the possible processes for chemotaxis. Protrusions in chemotaxing cells are formed by polymerizing actin and the key idea in this work was that waves of actin form an excitable medium. To model this observation Dr. Iglesias used a Fitzhugh-Nagumo framework. Noise induced transitions were added to the model and the rate at which noise-induced transitions occur followed from Kramer's theory. A major finding was that in a chemotaxing cell, the external cue biases the location of protrusions by lowering the threshold of excitability on one side. Bifurcation analysis revealed other dynamic behaviors; particularly, oscillatory behaviors where the cells probe homogeneously in space, rupturing, and unidirectional movement. The speaker used a synthetic chemically induced dimerization process to probe for bifurcations experimentally.

The Initial State of the Network
Aleksandar Haber (Northwestern University)
The speaker was interested system identification and establishing theoretical results for practical applications where classical control results fail. Often one cannot observe all states of a system and this is a barrier for network identification results. A key idea in this work is that one can view the identification problem as a matrix decomposition problem. Using the Implicit Function Theorem and Kantorovich theorem, the speaker was able to a guarantee solution to the identification problem in the case when the matrix is square.

Links between topology and controllability

Colin Campbell (Washington College)
Dr. Campbell began with a review of structural control and the motivating questions "assuming linear dynamics, how can we drive a network to the desired dynamic state through nonlinear perturbations?" In this talk the methods presented used topological properties, such as the number of sources and sinks and the degree distribution, of the network to make control decisions. Linear control theory was a key tool used to characterize the topological properties of a network. Dr. Campbell presented examples on when nodes could be directly and indirectly controlled in real networks.

Controllability and Identification of (Bi)linear Networks
Jorge Cortés (University of California, San Diego)
Dr. Cortes began with an overview of areas in network science where distributed control is utilized. The mathematical focus of this work was the analysis of network reachability and identification for bilinear control systems. The aims of the work were to understand how to efficiently drive the network to a particular state while only controlling a few components and using data to identify network structure when there are an undetermined number of latent nodes present. The speaker derived a Gramian-based lower bound for bounded inputs and this bound on minimum input energy justified the reachability metrics presented.

Unintended Actions
Adilson Motter (Northwestern University)
In this talk, Dr. Motter considered optimization in two scenarios: network controllability and metabolic networks. Additionally, the speaker was also interested in the robustness of an optimized solution to intended and unintended perturbations. The interest in robustness to perturbation arose because of the high dimensionality and nonlinearity of the metabolic networks considered. The speaker presented results on optimizing the number of controlled nodes in a network that are applicable to linear and nonlinear systems.

Detection of network changes via sampling
David Sivakoff (Ohio State University)
In this talk, the speaker focused on a detection method for alterations in how network sequences are generated. Changes in real and synthetic data can be found using this method can be either large-scale or localized. The sampling method presented by Dr. Sivakoff utilized is a sparse edge sampling with notable efficiency. More specifically, the method gains its efficiency by comparing snapshots of graphs which form a heterogeneous Markov chain and allow probabilistic techniques to do used.

Dynamics of complex biological systems determined/controlled by minimal subsets of molecules in regulatory networks
Atsushi Mochizuki (The Institute of Physical and Chemical Research)
Dr. Mochizuki began his talk by discussing structural theories that use only the information of the network, namely linkage logic in gene regulation networks and rate sensitivity analysis in chemical reaction networks. The talk focused on linkage logic and

the aim of the work was to reproduce diversity of gene expressions from a regulatory network. Dr. Mochizuki and his colleagues developed a method of studying dynamics from network structure alone by generalizing linkage logic. As an application reduced a complicated Ascidian network containing seven nodes encompassed the dynamics of 80 genes. The method found that attractors are detected by only one gene corresponding to a single feedback vertex.

Automation of big mechanism integration and analysis
Natasa Miskov-Zivanov (University of Pittsburgh)
In this talk, the speaker began with examples of how much more efficient tasks can be when automated to motivate how automation can be used in network building. The particular mathematical consideration was how one can understand and explain effects of many interacting components in networks. Dr. Miskov-Zivanov presented progress on the automation project which centered around three steps: extract information through mining, merge extracted information into a model and infer executable rules, and conduct analysis on graphs and pathways and simulations.

Characterizing heterogeneity in leukemic cells using single-cell gene expression analysis
Assieh Saadatpour (Harvard University)
Dr. Saadatpour's talk began with discussion of single cell biology, genomic sequencing and its importance in understanding leukemia, a cancer known for its variety of cellular phenotypes. To work towards understanding the heterogeneity observed in this cancer, quantitative PCR was used to collect on data on hundreds of genes and thousands of cells. The high-dimensionality of the data requires sophisticated techniques to uncover correlations and similarity between genes and cells. The first approach used by Dr. Saadatpour was t-Distributed Stochastic Neighbor Embedding (t-SNE), which projects high-dimensional data to two dimensions. Mapping the results of t-SNE to the normal hematopoietic cellular hierarchy identified distinct subpopulations of leukemic cells. Analyzing how genetic networks from the data compared to existing information, the speaker found the cells to be closer related to one subpopulation, granulocyte/monocyte progenitors. As a next step they are adapting other existing approaches for high dimensional data that create minimal spanning trees of cell populations.
Dynamics of network adaptation processes

Peter Csermely (Semmelweis University Medical School)
The speaker began with examples of how diminished resources lead to changes in network topology. The main biological consideration for the talk was the yeast interactome and how stress effects that networks of that system. Initial work produced the hypothesis that cycles of plasticity and rigidity, or changes in the number of attractors, in these networks form a general adaptation mechanism. Using methods from applied dynamics and analyzing network topology, Dr. Csermely was able to efficiently predict influential network nodes and the framework presented here can be extended to other networks.

Synchronization in Neuronal Oscillator Networks
Biswadip Dey (Princeton University)

Dr. Dey motivated his talk with examples of how synchronized activity is crucial for many neuronal behaviors. The objective of this work was to use knowledge of conditions for synchronization to gain a better understanding brain stimulation and measureable efficacy metrics for disease treatment. The mathematical framework considered was a network of Fitzhugh-Nagumo models with gap junction coupling. The speaker proved a sufficient condition for synchronization of these homogeneous semi-passive neuronal oscillators through the use of Lyapunov functions. Moreover, when applying heterogeneous stimuli to the network clustered synchronization was found to be possible.

WEDNESDAY, APRIL 13, 2016

Cell fate commitment as high-dimensional critical state transition revealed by single-cell resolution gene expression analysis in cell populations
Sui Huang (Institute for Systems Biology)
The speaker began with a review of cell differentiation and gene regulation networks. Moving from population averages of the transcriptome to single-cell resolution measurement that allows observation of changes in the population that previously might've been averaged out. Considering the data, the speaker found that the multi-modal distribution suggested multi-stability. Dr. Huang's group developed a framework where high-dimensional attractors in gene expression are well potentials in a landscape. Moreover, each well potential can be put into correspondence with cell types and development from an early cell type to a later cell type is thought to occur through bifurcation. The speaker used a rich qPCR dataset combined with the quasi-potential landscape framework to predict dynamic tipping points and development changes.

Reconciliation of genome-scale metabolic networks
Jason Papin (University of Virginia)
The speaker began by discussing the role of animal models in drug development. The mathematical objective considered in this talk was metabolic network reconstruction, where the stoichiometric matrix is not completely known. The speaker is interested in biomarker predictions of drug toxicity. To consider this problem, Dr. Papin's group introduced a method called TIMBR, an extension of parsimonious flux balance analysis. Using TIMBR, the speaker was able to predict organism-specific biomarkers, previously not possible with traditional or parsimonious flux balance analysis.

Investigating group behavior in dance: An evolutionary dynamics approach.
Kayhan Özcimder (Princeton University)
The speaker began with a discussion of social decision making in animal & human groups. This work utilized a dance experiment where five modules of dance techniques were given to dancers without a plan and 2-3 modules can be performed at a time. The experiment tracked the population performing moves from a module over time. The group used theory from evolutionary dynamics to study the group behavior, particularly, a replicator mutator model. Using applied dynamics, the group was able to characterize the changes in dance modules with a quintic pitchfork bifurcation.

Control and damage mitigation in signal transduction networks

Reka Albert (Pennsylvania State University)
Dr. Albert began with examples of how within-cell networks connect to cell behavior. The objective of this work was to find interventions that allow a return to healthy cellular behavior in the presence of dysregulation to the signaling network. Much of the work presented focused on developing a predictive Boolean model from qualitative data. More specifically, the modeling approach was Boolean modeling with stochastic updating and as an example the speaker presented a T cell survival model of T-LGL leukemia. Strongly connected components were found in this network and correspond to attractors dynamically. Controlling these components allows any attractor to be reached from a given initial condition.

Data-Driven Model Estimation in Biochemical Networks from Observed Equilibria
Yannis Paschalidis (Boston University)
The speaker began with a review of how metabolic activity can be measured in bacterial cells and motivated the question of how flux measurements can be used to determine cell objective functions. To consider the problem of determining an objective function from flux measurements and growth characterizations, Dr. Paschalidis's group developed a new framework, more general than traditional or inverse flux balance analysis. The variational inequality problem and associated theory presented in this talk allows for data-driven estimation from equilibria observed in the model in question. Moreover, the variational inequality framework allows for both parametric and non-parametric estimation. The speaker Presented a probabilistic guarantee that you will find an equilibrium to the optimization problem in the parametric estimation setting.

An evolutionary perspective of the p53 network
João Hespanha (University of California, Santa Barbara)
P53 plays a key role in tumor suppression on multicellular organisms. It is the most frequently mutated gene in human cancer. In humans, p53 is part of a network that mediates cell fate decisions such as initiation of cell-cycle arrest, DNA repair, and senescence or apoptosis. The network also includes MDM2, PTEN, and ARF. Homologs of the p53 gene have been preserved for over one billion years, but this is not the same for all other proteins, notably MDM2 is only present in vertebrates.

This yields two networks: one with MDM2 and one without. This talk explores the qualitative differences in the behavior of these networks and what intermediate behaviors could be observed in the evolution from one network to the other. By computing network bifurcation diagrams, the function of each module can be inferred. Though, even for "small" networks like p53 it is very hard to find all equilibria, even numerically using state-of-the art polynomial solvers of bifurcations continuation software. Instead, modular decomposition is applied to discover the structure of equilibrium points using a systematic method to break network of genes into modules. Results show an evolutionary path towards networks with an increasingly complex structure of multi-stability, which is conjectured to be associated with cell fate decisions.

Structure-based control of complex networks with nonlinear dynamics
Jorge G. T. Zanudo (Pennsylvania State University)

Many real-world applications in different fields involve controlling a network: i.e. disease spreading and social network. It is known that in order to control the internal state of a network, you drive it towards a desired state. However, structural control of real complex networks is harder to control than ER random networks and are degree distribution determined. Also, realistic dynamics for most complex networks are nonlinear.

Structure-based control approach for networks with nonlinear dynamics involves FVS and input control leading to attractor-based network control. Some similarities and differences between FVS control and structural control in real networks can be understood using Bowtie picture networks. This allows real networks to be easier to control than ER random networks, but still harder to control than degree-preserving random networks. It is found that cycles are crucial for nonlinear control.

On the perfect reconstruction of the topology of dynamic networks
Alan Veliz-Cuba (University of Dayton)
The network inference problem consists of reconstructing the topology or writing diagram of a dynamic network from time series data. If we know dynamical information of a function, what can we infer about the network structure of the function? Even though this problem has been studied in the past, there is no algorithm that perfectly reconstructs the topology of the network. Instead, we study the reconstruction coordinate-wise and create an algorithm to solve the network inference problem. This algebraic approach is guaranteed to reconstruct the topology of the dynamic network perfectly.

Identification of control targets of Boolean molecular network models via computational algebra
David Murrugarra (University of Kentucky)
Many problems in biomedicine can be characterized as control problems. The goal is to find strategies to change a disease or any other undesirable state of a biological system to another. The identification strategy's can be found using algebraic models for Boolean networks. Start with a molecular network, attractor landscape, identification control targets and consider computational changes you can make to the network. The potential control targets can be represented by a set of nodes and edges. Then, consider two types of control actions: node deletion and edge deletion. This approach exploits an algebraic representation of Boolean networks to encode the control candidates in the network. Secondly, a formula based on layers of canalization for Boolean networks in discussed. The hierarchy of the canalizing variables can be used for assessing the impact on the network dynamics as a results of a given control (deletion of edge). The upper bound for assessing the impact of the controllers is sharp.

Nonlinear Flows in Microfluidic Networks
Daniel Case (Northwestern University)

Microfluidics are tiny networks of pipes the width of a human hair. Precise control of flows through a microfluidic system, such as opening or closing of channels, is often achieved by nonlinear input from hardware, external to the system. Instead, the

Forchheimer effect of fluid inertia provides a local nonlinearity source. A network that incorporates this source can be constructed and analyzed for new and useful behavior. The microfluidic system can then be represented as a network and the flow through the network can be predicted by models of circuit analysis. This new network model also enables change of direction of flow through an intermediate channel in the network, observes an analog of Braess's paradox, and has evidence of negative hydraulic resistance.

Thursday, April 14, 2016

The advantages of nonlinearity in network control
Sean Cornelius (Harvard University)
In this talk, the speaker discussed two ways in which nonlinearity, instead of being an obstacle to the control of networks, becomes an asset to network control. First, the speaker showed how nonlinearity in the form of multi-stability allows one to systematically design control interventions that can deliberately induce ``reverse cascading failures", in which a network spontaneously evolves to a desirable (rather than a failed) state. Second, the speaker showed that nonlinearity in the form of time-varying dynamics unexpectedly makes temporal networks easier to control than their static counterparts, with the former enjoying dramatic and simultaneous reductions in all costs of control. This is true despite the intuition that temporality should fragment a network's structure, disrupting the paths that allow the directly controlled or ``driver" nodes to communicate with the rest of the network. Taken together, these parables shed new light on the crucial role of nonlinearity in network control, and provide support to the idea we can advantageously control nonlinearity, rather than letting nonlinearity control us.

Decentralized Hypothesis Testing on Graphs
Angelia Nedich (University of Illinois, Urbana-Champaign)
In this talk, the speaker considered the problem of distributed cooperative learning in a network of agents, where the agents are repeatedly gaining partial information about an unknown random variable whose distribution is to be jointly estimated. The speaker highlighted some interesting aspects of Bayesian learning and stochastic approximation approach for the case of a single agent, which has not been observed before and it allows for a new connection between optimization and statistical learning. The speaker then discussed and analyzed the general case where subsets of agents have conflicting hypothesis models, in the sense that the optimal solutions are different if the subset of agents were isolated. Additionally, the speaker provided a new non-Bayesian learning protocol that converges an order of magnitude faster than the learning protocols currently available in the literature for arbitrary fixed undirected graphs.

Control Minus Models
Thomas Wytock (Northwestern University)
Designing control strategies in engineered systems often requires reference to a mathematical description of the system in question. In molecular biology, such

mathematical descriptions are fraught with uncertainties to the point that they become unreliable.
In this talk, the speaker presented model-independent strategies, which rely on large numbers of observations to map out target states (desired basins of attraction or regions of high growth), and the response of the intracellular networks to gene perturbations (knockouts, knockdowns, and overexpression). The speaker demonstrated how such a model-independent scheme can be used to design perturbations that reprogram human cells toward a target cell type, or predict synthetic rescues in single-cell organisms. This model independent approach can hasten breakthroughs in systems biology by proposing interesting experiments.

Dynamics of large ecological systems: a random matrix approach
Stefano Allesina (University of Chicago)
In this talk, the speaker used the theory of random matrices to explain a series of studies on the stability of large ecological systems, which aimed at explaining the principal quantities that determine the response to perturbations. Specifically, the speaker used random matrix theory to study the interaction matrix, which is obtained as the composition of the community matrix and the adjacency matrix. Analytical results were obtained in some cases. The speaker showed how these methods can be applied to a diversity of problems in biology, and concluded with a list of challenges that need to be overcome to make this theory more applicable and complete. The main ecological questions are such as ``can you stabilize a large network by imposing a certain structure (modular or antimodular)?"

Using optimal control theory to select synchrony-promoting structures and dynamics that foster synchrony
Rachel Leander (Middle Tennessee State University)
In this talk, the speaker described how optimal control theory can be used to select network structures and dynamics that promote synchronization in a population of Kuramoto oscillators. The Kuramoto network is a tractable model of synchronization within a heterogeneous population of nonlinear-phase oscillators. Although the classical Kuramoto network is static and homogeneous, it can be adapted to allow for heterogeneous network structures and dynamics. The speaker showed that within a heterogeneous population, repulsion may have a synchrony-promoting function and time-varying networks can be more efficient than static networks at promoting synchrony.

Dynamics and control of autonomous Boolean ring networks
Daniel Gauthier (Ohio State University)
In this talk, the speaker showed an experimental approach that was developed to explicitly include both inter-node time delays and stochastic noise using digital logic elements on field-programmable gate arrays. Autonomous Boolean networks (ABNs) are commonly used to model the dynamics of gene regulatory networks. Most models do not account for time delays along the network links and noise, but these time delays are crucial features of real biological systems. The results of the experiments included transients that last billions of characteristic time scales and scale exponentially with the amount of time delays between nodes, a phenomenon known as super transient scaling.

Small, occasional perturbations applied to the time delays can force the transient trajectories to rapidly approach the asymptotic attractors.

Global Feedback Control on Centrality in Self-Organizing Systems
Nina Fefferman (Rutgers University, New Brunswick)
Evolutionary fitness is associated with social network positions. Networks emerge from individual behavioral choices such as proximity, grooming, aggression, mating, and communicating. The big questions in animal social networks focus on the individual, such as: can your genes determine your position in a network, do particular positions lead to better survival rate? Though, group success is also important since group participation is not without costs. Groups can attract predators, are in competition for food / mates, and transmit disease. There is individual-scale self-organization, direction and indirect fitness components, selection includes group benefits and costs, but individuals pass on their genes or not. This sets up a system of global feedback control, called multilevel selection in evolutionary theory.

To explore this mathematically, an abstraction is built and used as a computational experimental system. It is assumed that individuals make genetically determined "selfish" social affiliation choices. Initial hypothetical proxies of three measures of social status are used: degree, closeness, and betweenness. Once the diagraph is initialized, the three centrality measures for all of the vertices and entire network are computed. In each step, each vertex drops two of its existing out-neighbors and replaces them with two new ones. Over time, these structures converge, allowing the study of evolutionary selection on group task efficiency in already-social species. These results have direct implications for the evolution of social systems and provide intriguing potential mechanisms for general feedback control on global network outcomes.

Social Dynamics over Networks
Massimo Franceschetti (University of California, San Diego)
There has been much research in Network Science on structural properties. The next natural step is to look at agent interaction. First we look at answering the question: can we quantify emotional contagion through a network, such as Facebook? They consider status updates, classify semantic content of posts using LIWC, and count the daily fraction of posts with a work from a given semantic category. We use observational data only, without running the experiment. Instrumental variable regression is used, based on identifying an external variable, such as weather, that cannot be controlled but can be observed performing a "natural" experiment. Modeling and statistical analysis results show the existence of certain global social dynamics.

Secondly, to what extent can friendship ties between individuals predict who is at risk in an epidemic outbreak? Physical encounter is the most common vehicle for the spread of infectious diseases, but friendship relations often constitute the only available information. So, similarities and differences between the two networks are examined. While friendship networks are more likely to be available, encounter networks are only accessible in a context of "prediction in retrospect." It is shown that periodical and relatively infrequent reports of the infection spreading on the encounter network allow

prediction of the individuals at risk by simulating the epidemic on the friendship network. Using past encounters as a proxy of future encounters might also compliment friendship data.

Topological data analysis of contagion maps for examining spreading processes on networks

Mason Porter (University of Oxford)

Given a possible "social contagion," e.g. the spread of obesity, based on empirical data, we want to distinguish among genuine spread via social influence, homophiles, and environment. Control strategies depend on whether it's only one or a mixture of these. We study the spread of contagions by considering a noisy geometric network called "contagion maps." Nodes have an intrinsic location in space, with two types of edges: geometric edges and non geometric edges. By analyzing the topology, geometry, and dimensionality of manifold structure in these point clouds, insights to aid in the modeling, forecast, and control of spreading processes are revealed.

Fear in Networks: How social adaptation controls epidemic outbreaks

Ira Schwartz (Naval Research Laboratory)

Control and eradication of infectious diseases are main and important public health goals. Extinction is observed in networked populations when the infective population goes to zero; local extension in connected patches but reintroduced, but global extension is a difficult and rare event. Human behavior also modifies disease fade out, e.g. where the community learns to stay away from hospitals or suspicions govern people not to touch corpses.

Mathematically in real networks, nodes and links change in time-Dynamic networks. These node dynamics affect network geometry and network geometry affects node dynamics, creating a feedback loop interaction. This talk develops a general network formulation of extinction for a disease in a finite population. Vaccination and treatment models are used to quantify the effect of treatment programs on extinction rates. Extinction times in terms of bifurcation parameters can be predicted by optimal paths and optimal control is designed based on minimizing the action as a function of degree. It is found that for limited resources, larger treatment pulses less often are most effective.

Control of Contagion Processes on Networks

Kimon Drakopoulos (Massachusetts Institute of Technology)

There are local interactions of influence, dependences, contact and correlation that are well explained by networks, which provides a fundamental medium for propagation and diffusion of contagion. Most of the literature on control of contagion focuses on static strategies. In many applications, one has access to the network state in time, so more effective dynamic control polices can be developed. A novel dynamic priority that depends on network position and the state of network is defined. It shows cutoff dependence on humidity and strong predictions within regimes. Results show that travel impact is non significant and results are very sensitive to noise in travel data. This implies

policy implication within-state measures could be useful over travel restrictions to minimize the spread of contagions.

Friday, April 15, 2016

Self-organization in multi-agent swarms via pseudo-localization algorithms
Sonia Martinez (University of California, San Diego)

Control algorithms can be designed to model many multi-agent swarms, for example to force swarms of robots make certain shapes. Robotic and computing networks are unmanned vehicles and work under limited assumptions. The robots have to localize themselves in the swarm and use self-organization principles.

Properties and control of large-scale swarms include: finite set removal does not affect the groups macroscopic properties, macroscopic objectives are more easily specified as high-level functions, and controlling the state of each swarm element seems ineffective. This means we can view swarms as a discrete approximation of a continuous manifold. At every location, there is a robot communicating locally with others in its surrounding neighborhood. Algorithms are designed in the continuum domain with conservation of agent assumed. However, agents are not able to measure their positions relative to the frame, so the control laws are defined in terms of artificial coordinates that define a diffeomorphism between the spatial domain and a disk. A transformed objective is used, agents are approximately computed by pseudo coordinates, then the motion control law is defined using the coordinate approximation.

Fundamental limitations of Network Reconstruction
Marco Angulo (Universidad Autonoma de Queretaro)
Network reconstruction provides a first step towards understanding, diagnosing, and controlling very diverse networked systems. Network reconstruction problems start by knowing three things: desired property of the interaction matrix, temporal data of the system and certain knowledge of the coupling functions. However most existing algorithms do not perform significantly better than random guesses. Even well-established methods such as driving-response experiments can provide contradictory results for relatively simple networks.

Given temporal data and some knowledge of the system dynamics, we want to derive the necessary conditions on which network properties can be reconstructed. It is found that reconstructing any property of the interaction matrix is generically as difficult as reconstructing the interaction matrix itself. Thus reconstructing adjacency-pattern instead of edge weights does not make the reconstruction problem easier.

Discovery and Prioritization of Combinatorial Interventions in Signalling Networks
Andrew Gainer-Dewar (University of Connecticut Health Center)
Intracellular signaling networks play important roles in biological systems. The OCSANA is a helpful computational approach for discovering combinatorial

interventions in large-scale signaling networks. Recent advances in combinatorial algorithms have improved the time performance significantly and a new version of OCSANA will be available in the upcoming months. Additionally, chemo- and pharmaco-informatic data will be incorporated about the drug ability of specific nodes, helping to prioritize and eliminate proposed interventions.

Educational Programs

Joint 2016 US-Canadian Institutes Epidemiology Graduate Summer School: Mathematical Modeling of Infectious Disease (hosted at MBI) (June 13-22, 2016)

Graduate students from the mathematical and life sciences, public health, and related fields were encouraged to apply to the 2016 Graduate Summer School on Mathematical Modeling of Infectious Disease Spread, to be held at MBI. The program for this 10-day summer school will feature researchers from the mathematical and biological sciences, who will deliver lectures, case study presentations, and mentor the school participants in special project groups. The case study lectures will focus on public health issues, and will be open to the university community. During the summer program each student will work on a research project in a team of approximately five participants. Topics to be covered include: deterministic and stochastic frameworks for modeling disease dynamics; disease dynamics on social networks; metapopulations; host behavior and disease evolution; vector-borne diseases; zoonotic diseases; pathogen dynamics and co-infection.

The 2016 summer school will focus on the mathematical modeling of infectious diseases, a field that is growing in importance because of the many issues in disease spread and control arising from new or newly emerging diseases (e.g., SARS, Ebola, West Nile virus), and because new data sources are now available to study disease transmission, pathogen evolution, and the impact of the social behavior of hosts (e.g., genotyping databases, cell phone networks and air travel tickets, social networks). Capitalizing on new data sources to understand and control these impacts on disease spread requires detailed modeling of interactions amongst pathogens and hosts, the training of sophisticated modelers, and the development of new mathematics. This summer school will seek to prepare students to study such models in their future research.

No tuition is charged to summer school participants. Financial support for local expenses for 50 students was made available through co-sponsorship by the National Institute for Mathematical and Biological Synthesis (NIMBioS, Tennessee –Knoxville), the Army Research Office (ARO), the Fields Institute (Toronto), the Centre for Disease Modelling (CDM, York University), the Centre for Applied Mathematics in Bioscience and Medicine (CAMBAM), the Society for Mathematical Biology (SMB), and the Atlantic Association for Research in the Mathematical Sciences (AARMS). The Ohio State University and the National Science Foundation (DMS/NSF) have provided additional support.

Undergraduate Program (June 6 - August 12, 2016) [Mostly supported by a separate

NSF-REU grant]
This innovative program for 12 fully supported students will consist of three parts:

1. An introductory one-week program (June 6-10, 2016): Tutorials, computer labs, and short-term team efforts designed to introduce students to a variety of topics in mathematical biology.
2. An eight-week REU Program (June 13 – August 5, 2016): individualized research experience as part of a research team at one of the participating host institutions. This year's host institutions are: Arizona State University, Indiana University – Purdue University Indianapolis, New Jersey Institute of Technology, The University of Notre Dame, The Ohio State University, and Penn State University.
3. A one-week *Capstone Conference* (August 8-12, 2016): A student centered conference featuring talks and posters by students (usually 50 students participate) doing research in mathematical biology, keynotes by prominent mathematical biologists, a graduate studies recruitment fair, and other special features.

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. The MBI post-docs organize the annual *Workshop for Young Researchers in Mathematical Biology* (WYRMB) with two post-docs chosen to take the lead.
    c. Each year one MBI post-doc represents the post-docs on the MBI Colloquium Committee. The post-docs are in charge of taking colloquium speakers to lunch.
    d. An MBI post-doc is asked to give a talk at the annual SACNAS meeting; occasionally other post-docs speak at other diversity meetings.

MBI Postdoctoral Fellows

MBI NSF Supported Postdoctoral Fellows 2015-16. In [...] we indicate the next positions for Post-docs who have finished their stay at MBI in 2016

1. **Casper Woroszylo**
2. **Leili Shahriyari**
3. **Matt Oremland [**Process data scientist: Regeneron Pharmaceuticals, Inc.]
4. **Farrah Sadre-Marandi**
5. **Wenrui Hao** [Assistant Professor: Math, Penn State U]
6. **Kim Fessel** [Data Scientist: Breaktime Media, Boston]
7. **Karly Jacobsen** [Applying for job in industry]
8. **Reginald McGee**
9. **Richard Buckalew** [Assistant Professor: Math, Minnesota - Duluth]
10. **Jeff Gaither**
11. **Min Wang**
12. **Joy Zhou** [Assistant Professor: Math, Lafayette]
13. **Marcio Duarte Albasini Mourao** [Data Science Consultant/Database Engineer: U

Michigan, Consulting for Statistics, Computing and Analytics Research]

MBI Postdoctoral Fellow Hires to start in September 2016

1. **Punit Gandhi** (Physics, University of California at Berkeley)
2. **Colby Long** (Mathematics, North Carolina State University)
3. **Omar Saucedo** (Mathematics, University of Florida)
4. **Yangyang Wang** (Mathematics, University of Pittsburgh)

Post-doc Professional Development Seminar: This monthly meeting, led by **Mike Reed** and **Tony Nance,** gives 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.).

Short Course: In Autumn 2015 MBI Long Term Visitor **Ridgway Scott** (Computer Science and Mathematics, University of Chicago) presented an eight-lecture short course on *The Digital Nature of Biology* to MBI post-docs and visitors. More details about this course can be found at https://mbi.osu.edu/event/?id=991.

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.

Early Career Awards in 2015-16

ECA are competitively awarded annually by MBI to enable untenured tenure-track faculty to participate in MBI emphasis programs by **spending three-four months in residence at MBI.**

1. **Guang Lin**, Mathematics, Purdue University, Sep 25, 2015 – Dec 25, 2015
2. **Xueying Wang**, Mathematics, Washington State Univ, Jan 1 - May 31, 2016
3. **Casian Pantea**, Mathematics, West Virginia University, Jan 11 – May 10, 2016
4. **Rajeev Azad**, Biological Sciences, U North Texas, Jan 21 – May 18, 2016

Early Career Awards currently expected for 2016-17

1. **Lin Wan,** Chinese Academy of Sciences
2. **Juan Calvo,** University of Granada – Spain
3. **Nessy Tania**, Smith College
4. **Alan Veliz-Cuba**, University of Dayton
5. **Hye-Won Kang**, University of Maryland, Baltimore County
6. **Thomas Woolley**, Oxford University

Long Term Visitors in 2015-2016

1. **Fernando Antoneli**, Universidade Federal De São Paulo, Jan 23 – Mar 31, 2016
2. **Robert Eisenberg**, Molecular Biophysics and Physiology, Rush University

Medical Center, Aug 17 – Oct 16, 2015
3. **Cheol-Min Ghim**, Physical Biology Biological Physics, Ulsan National Institute of Science and Technology, Aug 10, 2015 – Jul 9, 2016
4. **Kesh Govinder**, Mathematical Sciences, University of KwaZulu-Natal, Mar 1 – Dec 20, 2016
5. **Jae Kyoung Kim**, Department of Mathematical Sciences, Korea Advanced Institute of Science and Technology (KAIST), Jan 11 – Feb 28, 2016
6. **Xiulan Lai**, Renmin University of China, Jan 14 - May 1, 2016
7. **Ka Yin Leung**, Mathematical Institute, Utrecht University, Jan 21 – Apr 16, 2016
8. **Tong Li**, Department of Mathematics, University of Iowa, Sep 15 – Oct 15, 2015
9. **Zhiming Li**, Central China (Huazhong) Normal University, Sep 18 – Dec 16, 2015
10. **Jinn-Liang Liu**, Cell Biology and Applied Mathematics, National Hsinchu University of Education, Aug 13 – Nov 1, 2015
11. **Bibo Lu**, Mathematics, Michigan State University, Aug 20 – Dec 20, 2015
12. **Philip Maini**, Wolfson Centre for Mathematical Biology, University of Oxford, Jan 26 – Feb 28, 2016
13. **Maya Mincheva**, Northern Illinois University, Jan 24 – Feb 27, 2016
14. **Duc Nguyen**, Mathematics, Michigan State University, Aug 20 – Dec 20, 2015
15. **Eddie Nijholt**, Mathematics, University Amsterdam, Feb 22 – Mar 25, 2016
16. **Tatiana Orlova**, Computer Science, U Chicago, Sep 21 – Dec 14, 2015
17. **Maciej Pietrzak**, Biostatistics, Ohio State University College of Public Health, August 2015 - August 2016
18. **Mason Porter**, Mathematical Institute, University of Oxford, Mar 19 – Apr 16, 2016
19. **Ridgway Scott**, Computer Science and Mathematics, University of Chicago, Sep 14 – Dec 12, 2015
20. **Yane Wang**, Shaanxi Normal University, March 2016 - March 2017
21. **Guowei Wei**, Department of Mathematics, Michigan State University, Aug 22 – Dec 12, 2015
22. **Jacek Wesolowski**, Department of Probability and Mathematical Statistics, Warsaw University of Technology, Apr 2-29, 2016
23. **Dexuan Xie**, Department of Mathematical Sciences, University of Wisconsin-Milwaukee, Aug 31 – Dec 15, 2015
24. **Hyunmo Yang**, Physics, Ulsan National Institute of Science and Technology, Sep 1, 2015 – June 30, 2016

Long Term Visitors currently expected for 2016-17

1. **Yane Wang**, Shaanxi Normal University
2. **Kesh Govinder**, University of Kwa Zulu Natal
3. **Boseung Choi,** Korea University Sejong Campus
4. **Bill Kalies**, Florida Atlantic University
5. **Abel Palafox Gonzalez**, CIMAT – Mexico
6. **Konstantin Mischaikow**, Rutgers University
7. **Tomas Gedeon**, Montana State University

8. **Kelly Spendlove,** Rutgers University
9. **Yury Garcia Puerta,** CIMAT – Mexico
10. **Marcio Gameiro**, University de Sao Paulo at Sao Carlos
11. **Xiulan Lai**, Renmin University – China
12. **Mason Porter,** Oxford University
13. **Yangjin Kim**, Konkuk University – Seoul, Korea
14. **Arnd Scheel**, University of Minnesota
15. **Blerta Shtylla**, Pomona College
16. **Philip Maini**, Oxford University

Short Term Visitors in 2015-2016

1. **Caleb Bastian**, Princeton University, Nov 30 – Dec 6, 2015
2. **Ariel Fernandez**, AF Innovation, Nov 3-8, 2015
3. **Giuliana Indelicato**, Mathematics, University of Torino, Sep 27 – Oct 12, 2015
4. **Reidun Twarock**, Mathematics and Biology, U York, Sep 25 – Oct 15, 2015
5. **Eunok Jung,** Mathematics, Konkuk University, June 12-22, 2016

Ohio State University Course Release Visitors in 2015-2016

Fall Semester

1. **Ching-Shan Chou** (Math)
2. **Avner Friedman** (Math)
3. **Chuan Xue** (Math)

Spring Semester

4. **Adriana Dawes** (Math)
5. **David Terman** (Math)
6. **Daniel Thompson** (Math)
7. **Joe Tien** (Math)
8. **Catherine Calder** (Statistics)
9. **Shili Lin** (Statistics)
10. **David Sivakoff** (Statistics)
11. **Yunzhang Zhu** (Statistics)

MBI hosted three seminars each semester weekly during non-workshop weeks: The MBI Colloquium, the Postdoc Seminar, and the Long Term Visitor Seminar.

MBI Colloquium

The MBI Colloquium brings in prestigious researchers from around the world to give high-level talks to non-expert scientists as well as spend time with the MBI post-docs. The 2015-2016 MBI Colloquium speakers were:

1. **Tim Elston**, Applied Mathematics, University of North Carolina Chapel Hill
2. **Haim Bar**, Statistics, University of Connecticut
3. **Seth Sullivant**, Mathematics, North Carolina State University
4. **Marsha Rosner**, Ben May Department for Cancer Research, University of Chicago
5. **Paul Stoodley**, Microbial Infection and Immunity, Ohio State University

6. **Santiago Schnell**, Molecular & Integrative Biology; Computational Medicine & Bioinformatics; Brehm Center for Diabetes Research; University of Michigan
7. **Marty Golubitsky**, Mathematics and Mathematical Biosciences Institute, Ohio State University
8. **Luis Carvalho**, Mathematics and Statistics, Boston University
9. **Andrew Noymer**, Public Health, University of California – Irvine
10. **Michael Summers**, Chemistry and Biochemistry, University of Maryland
11. **Domitilla Del Vecchio**, Mechanical Engineering, Massachusetts Institute of Technology
12. **Arni S.R. Srinivasa Rao**, Biostatistics and Epidemiology, Augusta University
13. **Giovanni Parmigiani**, Biostatistics, Harvard University
14. **Herschel Rabitz**, Chemistry, Princeton University

MBI Post-doc Seminar

MBI Post-docs and visiting post-docs give a research talk in this seminar each year. In addition to the 13 supported MBI post-docs two additional visiting post-docs, Maciej Pietrzak and Ruchira Datta, spoke in the MBI Post-doc Seminar.

MBI Long Term Visitor Seminar

With the number and scientific breadth of visitors (of all varieties) seen above, MBI added a 3rd seminar series featuring talks by MBI Long Term Visitors. The 2015-2016 MBI Long Term Visitor Seminar speakers were:

1. **Bob Eisenberg** (Molecular Biophysics and Physiology, Rush University Medical Center)
2. **Jinn Liang Liu** (Applied Mathematics, National Hsinchu University of Education)
3. **Gunjan Agarwal** (Biomedical Engineering, Ohio State University)
4. **Tong Li** (Mathematics, University of Iowa)
5. **Guowei Wei** (Mathematics, Michigan State University)
6. **Chuan Xue** (Mathematics, Ohio State University)
7. **Ching-Shan Chou** (Mathematics, Ohio State University)
8. **Guang Lin** (Mathematics, Purdue University)
9. **Dexuan Xie** (Mathematical Sciences, University of Wisconsin-Milwaukee)
10. **David Terman** (Mathematics, Ohio State University)
11. **Cheol-Min Ghim** (Life Sciences, Ulsan National Inst of Science and Technology)
12. **Philip Maini** (Wolfson Centre for Mathematical Biology, University of Oxford)
13. **Janet Best** (Mathematics, Ohio State University)
14. **Fernando Antoneli** (Mathematics, Universidade Federal de Sao Paulo)
15. **David Sivakoff** (Statistics and Mathematics, Ohio State University)
16. **Xueying Wang** (Mathematics, Washington State University)
17. **Mason Porter** (Mathematical Institute, University of Oxford)
18. **Joe Tien** (Mathematics, Ohio State University)
19. **Jacek Wesolowski** (Mathematical Institute, Warsaw University of Technology)
20. **Rajeev Azad** (Biological Sciences, University of North Texas)

MBI Visitor Reports

Fernando Martins Antoneli Jr.
Universidade Federal de Sao Paulo Sao Paulo - Brazil
Visiting period: January, 25 to April, 03 of 2016

During my visit to MBI I attended the following events of the Emphasis Semester on Dynamics of Biologically Inspired Networks: Spring 2016.

- Workshop 1: Dynamics in Networks with Special Properties. January 25, 2016 - January 29, 2016. (https://mbi.osu.edu/event/?id=896)
- Workshop 2: The Interplay of Stochastic and Deterministic Dynamics in Networks. February 22, 2016 - February 26, 2016. (https://mbi.osu.edu/event/?id=897)
- Workshop 3: Generalized Network Structures and Dynamics. March 21, 2016 - March 25, 2016. (https://mbi.osu.edu/event/?id=898)

I was one of the speakers at workshop on Dynamics in Networks with Special Properties giving a talk entitled \From motifs of regulatory networks to coupled stochastic systems" (https://mbi.osu.edu/video/player/?id=3816As a long term visitor, I also gave a talk "Mathematical Models for Gene Expression and Gene Regulatory Networks" at the Visitor Seminar in March of 2016 (https://mbi.osu.edu/event/?id=1048).

The participation in all those workshops was a great opportunity the meet several people working in mathematical approaches to many fundamental problems of biology and coming from many different backgrounds, such as, mathematics, statistics, computer science, physics and chemistry, on one hand, and several biologists interested in mathematical methods and techniques that could help them tackle the conceptual and data analytical challenges of modern biology, on the other hand.

The second goal of my visit was to initiate the collaboration with Martin Golubitsky (MBI and Department of Mathematics - OSU), which is part of the cooperation agreement between Ohio State University (OSU) and Fundac~ao para Amparo da Pesquisa do Estado de S~ao Paulo (FAPESP) Geometry and dynamics between Ohio and S~ao Paulo, under the sub-project entitled Dynamics on Networks. In this project we proposed to study two areas of network dynamics: the biological phenomenon of homeostasis and the framework for stochastics in coupled systems. Regarding the role of homeostasis in network dynamics, we were able to make some advances in the understanding of the structure of network preserving changes of coordinates in some special classes networks, which is an important step in the program for understanding homeostatis proposed in "M. Golubitsky and I. Stewart, Homeostasis, singularities and networks, J. Mathematical Biology (2016), DOI 10.1007/s00285-016-1024-2". Regarding the stochastic framework for coupled systems, the interaction with several specialists that were visit MBI during the period of my stay, especially for the workshop The Inter-play of Stochastic and Deterministic Dynamics in Networks was very helpful to clarify several conceptual and technical issues.

Finally, I think it is worth to mention that the environment provided by MBI is very stimulating, not only during the workshops when there are the participants, since usually there are several long term visitors at the same time and the interaction with researchers of dierent areas makes an enriching experience. I wish to thank MBI and FAPESP for their support of this visit.

Robert Eisenberg, August – November, 2015

My stay at the MBI was wonderfully productive and catalytic of new science. I participated in three workshops, two in areas adjacent to but distinct from my own, and learned of relevant work I wish I had known years ago, and interacted with many investigators, with whom I am now in touch. These include (more or less in order of my interaction with them), Guowei Wei, Ridgway Scott, Dexuan Xie, Duan Chen, Nathan Baker, Sharon Hammes-Schiffer, Teresa Head-Gordon, Bo Li, Julie Mitchell, Maria Shushko, Steve White, Simon Berneche, Benoit Roux, Claudio Berti, Wei Cai, Bert DeGroot, Maria Kurnikova, Ulrich Kleinekathoefer, Tai-Chia Lin, Chun Liu, Yuan-Nan Young, Marie-Therese Wolfram, and Sacco, Riccardo.

The public interactions (at the workshops) and new professional relations would not have occurred without the MBI and the help of its faculty and staff. But they are not the most important success of my visit.

The most important success is the work I was able to do with Jinn-Liang Liu and the new collaboration we started with Dexuan Xue. Both Jinn and Dexuan were long term visitors to the MBI and without the long term interactions we surely could not have done what we did.

The essence of our work is interdisciplinary. I bring long standing questions of biophysics and physiology to the table: how do ion channels work? How do these proteins, which are the target of a large fraction of drugs, and control so many biological functions, use their atomic structures to control macroscopic functions?

Ions in water and channels are charged particles that move essentially as would holes and electrons in semiconductors if they had finite diameter. The finite diameter is important because ions are roughly half the diameter of the channels they flow through and so they (nearly) saturate the space. But just as important as these steric effects is the imperative of electrodynamics. All charges and currents satisfy the equations of electrodynamics at all times and conditions. Ions in channels are no exception.

Semiconductor electronics has been able to remake our world in the last 60 years (with a roughly billion fold increase in capability) because it has learned how to write equations, and solve them, and how to do simulations, which always satisfy the equations of electrodynamics.

Jinn-Liang Liu is a theoretical physicist and applied mathematician with enormous experience in solving these equations. His community has some hundreds of websites putting forth packages for solving these equations, and the community has developed methods for solving these equations with great accuracy and satisfactory speed. Speed is necessary because of the huge size of digital circuits analyzed by the mathematics; accuracy is necessary because the enormous strength of the electric field demands precise calculation. Tiny errors of charge produce staggering forces that dominate problems. Tiny errors in conservation of current cannot be present if our computer technology is to work!

Combining the imperatives of electrodynamics, with the realities of finite size, and the needs for biological relevance produces severe demands on mathematics. Dexuan Xie is an accomplished analyst, as talented as anyone we have ever met, who is able to formulate and solve the combined Fermi Poisson models with speed and success beyond what Jinn-Liang and I can do. It took months to be sure we were communicating properly, but it only took Dexuan a few days to see a new way to do our analysis, and a week to produce a working draft of our first paper together.

Meanwhile, Jinn and I decided to tackle a biological problem of pivotal importance. A large fraction of the proteins in a human (and thus a large fraction of our genes) are devoted to channel like molecules called transporters, that move essentially every substance used by cells across the intestine, into the blood stream, and then later from the blood stream into cells. A common motif in these molecules is that they are branched (as I guessed and published they might be around 1992). The question is how do they work?

Jinn and I started with the atomic scale structure of one of these transporters (NCX) crucial in the control of cardiac contraction, in skeletal muscle control, and a key player in every system involving calcium ions (and thus in short term memory and learning in the hippocampus of the brain). Fortunately (and uniquely to our knowledge) there is a wonderful complete data set of everything this molecule does, thanks to my friend and colleague from UCLA days long ago, Don Hilgemann. So Jinn and I are writing a series of papers showing how NCX might work. The first paper was written at the MBI and takes the atomic scale structure and computes the electric and steric forces holding its substrates (sodium and calcium ions) into its very binding states. This paper represents the first physical model, as far as we know, of any transporter, that has full atomic detail, includes 'power supplies' and flow (i.e., gradients of electrical and chemical potential and concentration along with flux and current flow), and deals with biological function.

My time at the MBI thus led to immediate results with Jinn, forthcoming papers with Dexuan and Jinn, and new interactions of great promise. A great deal was done in two months, little of which would have happened without the MBI.

Jae Kyoung Kim (KAIST, Korea) January 17th to February 27th 2016

Summary of Activities as MBI Visitor:

Workshop Attendance:
Workshop 1: Dynamics in Networks with Special Properties

Current Topic Workshop: Modelling and Inference from Single Molecules to Cells
Workshop 2: The Interplay of Stochastic and Deterministic Dynamics in Networks

Seminars etc:
I attended several seminars in the MBI and the Department of Mathematics, and I also attended the Institute Partners Meeting.

I gave two talks:
Feb 5th: Process of Mathematical Modeling to Understand Biological Systems, Applied Mathematics Seminar
Feb 25th When do Michealis-Menten or Hill type propensity functions lead accurate stochastic simulations?, Workshop 2, MBI

Research Interactions:

Dr Hye-Won Kang (MBI workshop participant), **Dr Grzegorz Rempala** (MBI Deputy Director) and I discussed the problem of multiscale stochastic approximation method and began collaboration to improve the currently existing method so that it can be applied to more general multiscale stochastic systems. Recently, we got a simple method to resolve this issue and we has been writing the manuscript. Furthermore, **Thomas Kurtz** (MBI workshop participant) provided a wonderful feedback for our work.

Dr. Del Vecchio, Domitilla (MBI workshop participant) and **Herath, Narmada** (MBI workshop participant) and I have discussed about the validity of stochastic quasi-steady-state approximation throughout the workshop as we have used different approaches to solve this problem. Recently, I visited Domitilla's lab at MIT to discuss about the collaboration and writing a grant proposal together.

Dr. Cheol-min Ghim (MBI Visitor) and I have begun to explore the possibilities of using my stochastic QSSA method to accelerate the simulations of his mathematical model describing the stochasticity in gene transcription and translation. This collaboration is still ongoing.

With **Dr. Marty Golubitsky** (MBI Director), I discussed to find a biological example which can be applicable with his recent theoretical analysis method for identifying homeostasis of the system. In particular, we have discussed how his method can be used to investigate the temperature compensation of circadian rhythms. This collaboration is ongoing.

Zhiming Li: September 20, 2015 - December 15, 2015

During these three months at MBI, I did the following things:

1. I participated four workshops as scheduled of MBI emphasis semester on mathematical molecular biosciences fall 2015.
2. I talked with people in MBI about my recent work and learn a lot useful information and knowledge.

3. I did some work on protein classification by using persistent homology and machine learning method. Based on this work, I further did some research on topological entropy. I would try to find the differences between traditional conformation entropy and topological entropy.

These three months staying at MBI was a tremendous experience. Here, I was surrounded by great professors and postdoctors who provided me with lots of opportunities to think and express on my interested topics. I enjoyed different platforms to equip myself academically, socially and interactively. These experiences broadened my horizons, enriched my knowledge and helped me to move forward.

Thank you MBI for providing me with lots of opportunities to challenge myself and lay a solid foundation for my future work.

Jinn-Liang Liu, August – October, 2015
National Hsinchu University of Education, Taiwan

My stay at the Mathematical Biosciences Institute was the most wonderful, inspirational, and catalytic research activity that I have ever had in 20 years. The MBI director **Marty Golubitsky**, deputy director **Tony Nance**, and their colleagues have provided a remarkable scientific leadership and environment to the mathematical biosciences community by offering diverse and interesting programs and thoughtful and hospitality administrative helps for all visitors. The MBI, its people, the Ohio State University campus, and of course the champion Buckeyes have impressed me, a long term visitor from Taiwan, in this early Fall so profoundly that I'll never forget.

Bob Eisenberg, my dear collaborator and mentor who made this visit possible, made my stay even more marvelous and unforgettable by his seemly unlimited knowledge in biology, physics, American culture, and football conveyed in our countless conversations during the visit, thanks to MBI for arranging us to share the same office and live in the next-door apartments. We have developed a continuum-molecular theory --- Poisson-Nernst-Planck-Fermi theory --- in the last three years (with 5 journal papers) for simulating ionic flows in biological ion channels under physiological or experimental conditions by treating ions and water of any diameter as spheres with interstitial voids and polarization of water. The theory can compute electrical and steric potentials from all atoms in a protein and all ions and water molecules in channel pore while keeping electrolyte solutions in the extra- and intracellular baths as a continuum dielectric medium. During the visit at MBI, we have written our first paper on the sodium calcium exchanger (NCX) that is critical for calcium homeostasis necessary for the development and survival of all animals. This starts a new phase of our collaboration in a very interesting, important, and challenging project on the NCX dynamics that we hope we can understand the working mechanism of NCX in both physiological and pathological conditions.

Dexuan Xie, a new friend and ongoing collaborator whom I met at MBI, and I cooked Chinese dishes for each other in many dinners and talked about our ideas on the Fermi distributions and the nonlocal effects of electrolyte solutions. We are now working on a

mathematically more rigorous and physically more intuitive theory that we call the nonlocal Poisson-Fermi theory in which the Fermi distribution can be shown as a unique minimization of a new modified free energy functional and the nonlocal electrostatics is based on a convolution of the displacement field in Maxwell theory. We are also extending from our separate biological interests, namely ion channels and enzymes, toward each other's. We hope we can visit each other every year to continue our friendship as well as scientific collaboration.

Ridgway Scott gave very interesting lectures on data mining and drug design. The binding mechanism and hydrophobic and nonlocal electrostatic effects of enzyme proteins, which play important roles in enzyme activities and thus in drug design, may be investigated by the nonlocal Poisson-Fermi theory. Dexuan is also an expert in this field and we shall work on this in our future collaboration. I find **Ridgway**'s pending new book *Digital Biology* very informative and interesting, which is a good source for students or workers in mathematics as well as biology to learn fundamental physics and mathematics in molecular based proteins.

Guowei Wei, who is the head of the Mathematical Molecular Biosciences Program of this year MBI Emphasis Program, initiated our visit to MBI. **Gouwei**'s work on numerical mathematics of Poisson-Boltzmann and Poisson-Nernst-Planck models of molecular proteins has been an important and validating source of my investigations of ion channels and PNPF theory since 2011. His talk at MBI on the geometric PDE and multiscale modeling of biomolecular systems continues to motivate me with many new ideas.

I also met a lot of workers in mathematical biosciences at MBI who were only known to me through the literature or not. I expect to see them in future activities at other places. For example, **Bo Li** is coming to Taiwan next week and I shall meet and learn from him at 2015 NCTS Winter School at National Taiwan University, organized by **Tai-Chia Lin** who also gave a talk at the MBI Emphasis Workshop on Modeling and Computation of Transmembrane Transport in Nov. 16 – 20. Unfortunately, I was back to Taiwan on Nov. 3 and missed all the talks of the workshop that I found very interesting from MBI's website --- a nice and informative website for all people being there like me. I also expect to see **Chun Liu** next week at NTU, who gave a talk at the MBI workshop too. **Chun** and **Bob** have been and continue to be inspirational leaders, mentors, and friends to more than a dozen of colleagues and many more students in Taiwan, who are working on mathematical physiology, since the first workshop organized by **Tai-Chia** in early 2010. **Tai-Chia** leads and contributes significantly in mathematical biosciences in Taiwan by organizing at least one international conference or workshop and many local seminars and workshops each year. Taiwan's teams are growing and active and will be more interactive with our American colleagues and students in this research area.

The 2014 champion Buckeyes are amazing. I watched two games (playing Hawaii and W. Michigan) with **Bob** and almost 110,000 other people each game at Ohio Stadium. The winning streak of Buckeyes was 21 by the time I left Columbus on Nov. 1. It cost me $203 for the first game and nothing for the second (with a great seat) thanks to **Tony**'s two free tickets as he went to his son's soccer game that day. The net income for each home game

is approximately $5.75 million and the salary of the OSU head coach **Urban Meyer** is $5.86 million according to the campus newspaper Lantern. For a Taiwanese, I can only say ``Wow''.

I shall enjoy my OSU memory and MBI inspiration forever.

Bibo Lu: September 15, 2015- December 15, 2015

During the last three months at MBI, I participated various research activities and made some research on cDNA image processing, which will be listed below.

1. I took part in several workshops in MBI 2015 fall emphasis semester on mathematical molecular biosciences. During the workshop, I focus some talks and posters which inspirited me with some new views.

2. I participated Science Sunday activities three times which sponsored by MBI partly. The experts from other fields shown some advances in related research.

3. I made some researches on cDNA image processing. More precisely, I proposed a new method for cDNA image segmentation. Compared to some previous method, the new method used a modified level set based technique in local grid, instead in a whole image. The basic experimental results show the performance of the new method.

4. Based on the segment results, some feature will be extracted in near future and the subsequence research includes the correlation calculation and data analysis.

Though some research will be carried on after I leave MBI, I thank MBI for giving me a chance to visit in this semester. And I indeed enjoyed many things provided by MBI, such as excellent work condition, idea exchange platform, and chance to talk with some famous professors and postdoctors, and good organization ability which relies on every staff in MBI.

Professor P. K. Maini FRS
Wolfson Centre for Mathematical Biology

Dear Marty,

Thank you for being a wonderful host during my 5 week stay as an MBI Visitor. I attach a brief report on my activities and am happy to supply more details if necessary.

As you know, the field of mathematical biology has undergone such dramatic changes that it is unrecognizable from what it was 10 years ago. Not only is it now truly interdisciplinary, it is also *inter*disciplinary as we realize that the traditional deterministic applied mathematics approach is insufficient and we need to incorporate ideas from stochastic analysis, statistics, pure mathematics, network science etc. into our modelling

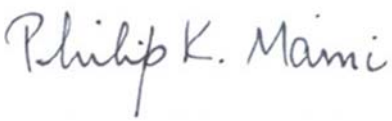
and analysis. The MBI is unique in providing a setting in which this can take place and, indeed, it has been instrumental in facilitating this leap in the subject.

I would also like to say that the MBI staff were, as usual, so very helpful and took care of every detail so that all I needed to worry about was my mathematics. I travel extensively but no institute can compare with the MBI in terms of level and quality of support.

The MBI is a very special place and I thank you again for giving me the opportunity to spend an extended period of time here.

With very best wishes,

Yours sincerely,



Professor Philip K Maini FRS, FIMA, FRSB, SIAM Fellow
Statutory Professor of Mathematical Biology
Director, Wolfson Centre for Mathematical Biology
Professorial Fellow, St John's College, Oxford
Editor-in-Chief, *Bulletin of Mathematical Biology* [2002-2015]

P.K. Maini: Summary of Activities as MBI Visitor: January 26th to February 28th 2016

Workshop Attendance:
Workshop 1: Dynamics in Networks with Special Properties
Current Topic Workshop: Modelling and Inference from Single Molecules to Cells
Workshop 2: The Interplay of Stochastic and Deterministic Dynamics in Networks

Seminars etc:
I attended several seminars in the MBI and the Department of Mathematics, and I also attended the Institute Partners Meeting.

I gave two talks:
Feb 2nd: Case Studies in Modelling Collective Cell Motion in Biology, MBI
Feb 18th: Case Studies in Mathematical Modelling of Solid Tumours, Applied Mathematics Seminar

Research Interactions:

On two previous trips to the MBI I started a collaboration with **Professor Mark Foster** (Department of Chemistry and Biochemistry, OSU). This project involves developing models to understand how cooperativity arises in the binding of the protein TRAP which regulates tryptophan production in certain bacterial species. I asked another collaboration

of mine, Professor Don Kulasiri (Head of the Department of Wine, Food and Molecular Biosciences,
Lincoln University, Christchurch, New Zealand) to work with us on this problem and he now has a graduate student doing her PhD on the modelling side. Through a number of meetings on this trip (and skype call to New Zealand) we were able to set up a project plan and arrange for the student to visit Professor Foster's laboratory for an extended stay.

Dr Leili Shahriyari (MBI postdoc) and I discussed the problem of regulation in the intestinal crypt. She is developing ordinary differential equation models and stochastic models to investigate how stem and differentiated cells respond to wound healing to re-establish homeostasis. I worked with her on developing more realistic feedback models.

Dr Rajeev Azad (MBI Visitor) and I have begun to explore the possibilities of using his bioinformatics techniques to extract network structures in the different phenotypic cells that my research group identified in a joint project on cranial neural crest cell movement with Professor Paul Kulesa's laboratory at The Stowers Institute for Medical Research, Kansas.
We will continue to pursue this project with Dr Azad during my upcoming trip to The Stowers.

With **Dr Ruchira Datta** (MBI and OSU James Comprehensive Cancer Center postdoc), I discussed how the bioinformatics data she will begin to analyse on gene regulation in response to stromal interactions could be used to inform mechanistic models of branching in the breast duct and also models for tumour invasion which could significantly extend some preliminary modelling studies carried out in my group.

During the Current Topics Workshop I met up with **Dr Anastasios Matzavinos** (Brown University) and we discussed a possible new collaboration. With Professor Helen Byrne (Oxford) I have been working on cancer angiogenesis where we assume Poiseuille flow, as an approximation to the Navier-Stokes equations, for computational simplicity. However, Dr Matzavinos has developed a new computational technique for Navier-Stokes which is very efficient and we intend to work with him to implement this into our model.

Dr KaYin Leung (MBI Visitor) met with me for career advice, in particular she wanted to know how to establish stronger links with experimental groups and how to set in place a career structure which would give her the flexibility to pursue deep mathematical questions while also developing applicable models.

Duc D. Nguyen

I visited Mathematical Molecular Biosciences (MBI) in four months, starting August 17th, with a goal of being exposed to the novel and hot research directions and meeting many famous mathematicians and biologists. I really appreciate the opportunity of staying in MBI to learn new things and do my research. During my stay, I shared an

office with two friendly MBI Post- docs. I was equipped with essential resources, such as computers, printing machine, kitchen, housing support, etc. to enhance my research and boost my morale. MBI staffs were very useful, they were always ready to help when I needed.

Also, having lunch together with MBI people was also great. Besides attending many useful seminars and colloquium talks, I participated in emphasis program, Mathematical Molecular Biosciences, including four workshops, namely, Geometric and Topological Modeling of Biomolecules, Multiple Faces of Biomolecular Electrostatics, Modeling and Computation of Transmembrane Transport and Mathematical Challenges in Drug and Protein Design. The four month visit allowed me to conveniently and fully followed all the talks in workshops. As a result, I got an article entitled "Accurate, robust and reliable calculations of Poisson-Boltzmann solvation and binding energies" ready to be submitted. In a word, I thank MBI for visiting programs and hope to have another chance to be back to MBI to experience such wonderful research environment again.

Casian Pantea (West Virginia University) Spring 2016 MBI

1. Generalization of Birch's theorem – with G. Craciun (UW Madison) and S. Mueller (Austrian Academy of Sciences). Birch's theorem provides much insight into the remarkable stable be- havior of mass-action complex-balanced reaction systems. On the other hand, its application depends critically on the polynomial form of mass-action dynamics. In this project we aim to extend Birch's theorem so that it can be applied to more general classes of kinetics. The result would have implications beyond reaction networks (for example, Birch's theorem is a key ingredient in the theory of maximum likelihood estimates for log-linear models). We made significant progress on this project during G. Craciun's visit at MBI in January. We expect to have a paper submitted by Fall.

2. Persistence of subnetwork multistationarity – with M. Banaji (Middlesex University). Most of the current work on multistationarity of reaction networks focuses on constructing necessary conditions for the existence of multiple positive steady states. On the other hand, very few sufficient results for multistationarity are known. In this project we aim to construct an inductive algorithm for proving existence of multiple positive steady states by analyzing conditions that guarantee that (multiple) equilibria of subnetworks persist when new species and reactions are added. This project was started in January during M. Banaji's visit for the fi MBI workshop of the year. We have a few very promising partial results, and we expect to submit a paper by the end of the year.

3. Nondegeneracy of equilibria – with A. Shiu (Texas A&M) and B. Joshi (California State San Marco). Lifting equilibria of a subnetwork to equilibria of the larger network involves checking a certain kind of nondegeneracy of the steady state. This is a rather involved computation that is generally done in a case by case fashion. In this project we aim to show that certain conditions on the network structure alone imply the needed non-degeneracy. The project started while A. Shiu and B. Joshi visited MBI during the fi st workshop in 2016.

4. Identification of rate constants in stochastic reaction networks – with Casper Woroszylo (MBI). This is a project that started with the question: is it possible for a certain reaction network to be assigned two diff t sets of rate constants such that the resulting stochastic processes be the same? It is known that in the deterministic case this is possible, and the networks that allow for this are precisely those whose structure satisfies a certain condition. Preliminary work on this question shows that this phenomenon is in fact not possible in the stochastic setting. But since the deterministic dynamics is achieved as a certain limit of the stochastic model, it is an interesting question to study how the non-identifiability condition in the deterministic case arises in the limit from identifiable systems.

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Xueying Wang (January-May, 2016)

My visit at MBI has been terrific, and it is very productive scientifically. During this visit, I attended all the MBI workshops and visitor seminars, and some of postdoctoral seminars and colloquiums; I gave one talk in MBI Visitor Seminar (March 15) and another talk in Applied Math Seminar (April 7), Department of Mathematics. These activities bring a great opportunity for me to meet experts in the fields, and start collaborations in interdisciplinary research.

Stochastic networks
One project aims to study frequency amplification in feed-forward networks due to resonance and noise, in collaboration with Marty Golubitsky, Jim Keener and Fernando Antoneli. The current idea is to analyze the stationary distribution of a Hopf oscillator subject to different types of noise and seek the linkage between stochastic bifurcation and the corresponding forced response curves in deterministic case.

Computational Neuroscience
One project is to study cortical inhibition in response to visual stimulus. With Dave Terman, Joshua Goldwyn and Joe Travers, we develop biological realistic models to study GABAergic modulation on solitary tract. Our findings indicate that afferent responsiveness and inhibitory modulation vary markedly in subclasses of excitatory and inhibitory rNST (rostral nucleus of the solitary tract) neurons. More specifically, activation of GABAergic circuitry can produce both subtractive and divisive effects.

Infectious Disease Modeling
Project 1: global dynamics of cholera epidemics – with Kazuo Yamazaki. Global threshold result is established for a reaction-advection-diffusion cholera epidemic model by using the basic reproduction number R0. We prove that if $R0<1$, disease will die out and the disease-free equilibrium is globally attractive; if $R0<1$, the disease will persist uniformly. Our findings may suggest efficient implications for the prevention and control of the disease.
Project 2: spread of SIR infection dynamic invasion with environmental reservoir on networks – with KaYin Leung and Pauline van den Driessche. Binding side models are formulated to investigate the disease dynamics of a water pathogen. These network models contain three distinct levels: binding sites, individuals and population. Our work characterizes population-level epidemiological quantities such as the basic reproduction number, the final size and global stability of the endemic equilibrium in certain case. We are now doing numerical simulations to study the impact of indirect transmission and intrinsic growth of pathogens on biding site and individual levels.
Project 3: disease invasion and awareness on complex networks – with Joe Tien and

Matthew Osborne. To address the dynamical interplay between awareness program and disease spreading, we consider two types of models: compartmental models (which is on the population level) and multi-layer network models (which aims to capture the complex dynamics). Using bifurcation theory to analyze compartmental models, we obtain interesting finding on the impact of awareness (human regulation) of disease invasion. We currently focus on network models and seek the connection between these two types of models.

Traveling Wave Solutions
I have been working on (1) the existence of traveling wave solutions and minimal wave speed; (2) exponential estimate and non-existence of traveling waves for a family of non-cooperative reaction- diffusion systems, in collaboration with Adrian Lam and Tianran Zhang. By analyzing the characteristic equation, we determine the minimal wave speed. A pair of lower and upper solutions are constructed and Schauders fixed-point theorem is applied to prove the existence of semi-traveling wave solutions for a auxiliary systems. The existence of traveling wave is verified by limit arguments and non-existence is argued by contradiction using Laplace transform.

Professor Dexuan Xie
Department of Mathematical Sciences -University of Wisconsin, Milwaukee, WI

I visited the Mathematical Biosciences Institute (MBI) at the Ohio State University, Columbus, Ohio, from September 1, 2015 to December 15, 2015. As a long-term visitor, MBI provided me with local housing, office, computer, and access to the University library. MBI is one of the best places in the world for applied and computational mathematicians to carry out research in mathematical biology. Especially, the MBI 2015 fall program matched perfectly my current research interests. It brought together researchers from mathematics, chemistry, physics, biology, computer science, and bioengineering to exchange new ideas and new results related to biomolecular modeling and simulations.

During my visit, I attended six workshops. I also attended various seminars held in MBI, some applied mathematics seminars in the department of mathematics at the Ohio State, and one special course taught by Prof. Ridgway Scott --- a MBI long-term visitor from the University of Chicago. Moreover, I met many outstanding scientists and researchers from different countries and different fields. I particularly enjoyed the meetings and discussions with several MBI long-term visitors, through which I have established some connections with them. Especially, I started to work on a new research project together with Prof. Robert Eisenberg (Rush University Medical Center, Chicago) and Prof. Jinn-Liang Liu (National Hsinchu University of Education, Taiwan). I learnt a lot from many conversations with Professors Guowei Wei, Guang Lin, Gheol-Min Ghim, and Chuan Xue, etc. on their research projects. Through the workshops, seminars, and other activities, my knowledge and research areas have been significantly expanded. My working experience at MBI is short but will have an important impact on my future research and teaching.

The main accomplishments I made during my MBI visit are listed as below:

1. Set up a research project to work with Prof. Bob Eisenberg and Prof. Jinn-Liang Liu. The project is to study a new ion channel model and related numerical solvers. A new paper has been started to draft by Jinn. Bob will take a shore visit to me in Feb. 10 to 13, 2016 to discuss the project and the paper. Three of us will meet in an international conference in China in the June of 2016 to continue our project and paper study.

2. Submitted a new NSF research proposal to the Mathematical Biology Program, NSF on Nov. 16, 2015. This proposal was written during my visit. Prof. Ridgway Scott is the PI for the University of Chicago for this collaboration research project.

3. Submitted a research proposal to the Clinical and Translational Science Institute of Southeastern Wisconsin (CTSI) on Dec. 14, 2015. The proposal was completed in MBI. Co-PI is Prof. Ranjan Dash from the Medical College of Wisconsin.

4. Presented one talk in the MBI workshop on Mathematical Challenges in Drug and Protein Design on Dec. 10, 2015 (see https://mbi.osu.edu/event/?id=826#schedule for the abstract of the talk).

5. Presented an invited talk in the MBI Visitor Seminar on Dec. 1, 2015 (see https://mbi.osu.edu/event/?id=1000 for the abstract).

6. Presented a talk in the Applied Math. Seminar in the Department of Mathematics, Ohio State University on Oct. 7, 2015.

7. Worked on three research papers. Two of them were published on January, 2016.

Here are the six workshops that I attended and the three papers I completed during the MBI visit:

Six workshops:

1. Workshop on Omics Data Analysis, 9/16-9/18, 2015.
2. Workshop 1: Geometric and Topological Modeling of Biomolecules, 9/28-10/02, 2015.
3. Workshop 2: Multiple Faces of Biomolecular Electrostatics,10/12-10/16, 2015.
4. CTW: Uncertainty, Sensitivity and Predictability in Ecology: Mathematical Challenges and Ecological Applications, 10/26-10/30, 2015.
5. Workshop 3: Modeling and Computation of Transmembrane Transport, 11/16-11/20, 2015.
6. Workshop 4: Mathematical Challenges in Drug and Protein Design,12/07-12/11, 2015.

Three papers:

1. D. Xie and J. Ying: A New Box Iterative Method for a Class of Nonlinear Interface Problems with Application in Solving Poisson-Boltzmann Equation, Journal of Computational and Applied Mathematics, Available online 14, Jan., 2016. [pdf]
2. Y. Jiang, Y. Xie, J. Ying, D. Xie, and Z. Yu: SDPBS web server for calculation of

electrostatics of ionic solvated biomolecules, Molecular Based Mathematical Biology, Volume 3 (1), Nov. 2015.
3. D. Xie, H. Volkmer, and J. Ying: Analytical Solutions of Two Nonlocal Poisson Dielectric Test Models with Spherical Solute Region Containing Multiple Point Charges, submitted, Nov. 2015.

Hyunmo Yang, Ph.D candidate, Physics, UNIST
09/01/2015 – 06/30/2016

I'm the person who is interested in exploring a biological system with the perspective of statistical physics, which is strong tool to look at and exploring complex and interacting systems. Biological phenomenon, from the scope of chemical-chemical interactions to the large ecological systems, can be thought as complex systems based on abstracting components of a system into mathematical variables with describing interactions among them as functions depending on them. In that sense the power of mathematical way of thinking is very important and I was so glad when my advisor suggested to me to visit the MBI with him, since it was very good chance to learn more and experience the world beyond the texts. Now I would like to say the time at the MBI was so much great and this is brief report about how I spent my time at the MBI during the last 10 months as a visiting scholar and how I felt about this experience.

Workshops & Seminars – The best thing during the visiting period was that I could join lots of workshops and seminars at the MBI and those were great time to learn more things beyond the text through communicating with other people. One of the main interests that I have in my mind is complex systems in biology in terms of complex networks based on the graph theory. Luckily during my visiting period there were series of workshops on complex network related topics, especially about dynamical systems in biology. Before I went to the MBI I was working on the evolutionary game dynamics on complex networks, so that I had enjoyed all of related workshops. Those of workshops were very much informative and also good chance to communicate with the people who are expert at their studies. I could say that lots of ideas for the future study came from those workshops.

From the seminars, which were invited talks, talks from other visitors at the MBI, and MBI postdoc seminar, I could listen stories beyond my interests and from that my perspective became wider. There was also a special seminar once in a month, which is the professional development (PD) seminar for the MBI postdocs, and I was impressed because that series of seminar were all about subject related to the future career and how to improve personal skills such as presentation, communication with others, writing papers, etc., which are "theoretically" understood but hard to make improvement with real action for me. One day in PD seminar I volunteered to give a presentation about my research topic, which was my first English presentation in front of English speakers, and feedbacks from professor Tony Nance, professor Michael Reed and other postdocs were very helpful later preparing for the presentation at the APS march meeting 2016. Not only presentation skills but also "how to communicate with other scientific people in English" was one that I could dramatically improve during the visiting period with help of PD seminar.

Personal study – When there were no workshops and no seminar I spent my time for my personal study, the evolutionary game dynamics. The MBI provided nice office, personal computer, and also office supplies. Discussions with other postdocs, especially with Leili who was officemate and cancer modeling expert, were greatly helpful to improve my personal study. With the results from the study I attended to the APS in march 2016 at Baltimore and now summarizing the contents to submit a paper. I thanks to Leili and others for fruitful discussions.

Summer school – Just before I left MBI I could have the chance to join the US-Canadian institutes epidemiology summer school, from 13th to 22nd of June. During 10 days of school intensive and informative lectures about epidemiology and how to approach to epidemiology related research were given with practical assignments. Also I had to participate the group project. It was tough to learn new things which was not familiar to me within short time, but it was worthwhile to keep discuss with other members and try to understand different perspectives, since all of group members are from different study fields. Simply it was really fun and worthy.

I would like to say that the time at the MBI was truly priceless and will be helpful for my future career. People who I met at the MBI were all bright and professional. I wish I could be like them one day in the future. For the last, I appreciate to the directors of MBI, especially professor Marty Golubitsky and professor Tony Nance, who encouraged and allowed my visiting with financial support. During the period I was helped by MBI postdocs, especially from Casper Woroszylo, Min Wang, Leili Shahriyari, Wenrui Hao, and Karly Jacobins. With their help and kindness, I could enjoy the time and step forward during the period.

MBI Series Books Published by Springer in 2015-16

The Mathematical Biosciences Institute Lecture Series
Series Editors: **Marty Golubitsky, Michael Reed**
http://www.springer.com/series/13083

Volume 1: *Stochastics in Biological Systems*, Editors: **Michael Reed, Richard Durrett**

Volume 1.1 *Branching Process Models of Cancer* by **Richard Durrett**
Volume 1.2 *Stochastic Analysis of Biochemical Systems* by **David F. Anderson, Thomas G. Kurtz**
Volume 1.3 *Stochastic Population and Epidemic Models* by **Linda J.S. Allen**
Volume 1.4 *Stochastic Models for Structured Populations* by **Vincent Banseye, Sylvie Meleard**
Volume 1.5 *Stochastic Neuron Models* by **Priscilla E. Greenwood, Lawrence M. Ward**
Volume 1.6 *Probabilistic Models of Population Evolution* by **Etienne Pardoux**

MBI Institute Partners in 2015-2016

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 64 Institute Partners, including the withdrawal of Rutgers University at Camden and the addition of two IPs in 2015-2016:

1. University of Chicago
2. University of Wisconsin-Milwaukee

Continuing Institute Partners:

3. Arizona State University
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 Ciencia
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 (UNAM)
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 Cincinnati
41. University of Exeter
42. University of Georgia
43. University of Glasgow
44. University of Houston
45. University of Iowa
46. University of KwaZulu-Natal
47. University of Maryland
48. University of Maryland Baltimore County
49. University of Miami
50. University of Michigan
51. University of Minnesota
52. University of Notre Dame
53. University of Nottingham
54. University of Oxford
55. University of Pittsburgh
56. University of Southern California, Los Angeles
57. University of Twente
58. University of Utah
59. University of Washington
60. University of Waterloo
61. University of Wyoming
62. Vanderbilt University
63. Virginia Commonwealth University
64. Virginia Polytechnic Institute and State University

Public Lecture series

MBI continued to be instrumental in the Science Sundays Public Lecture Series at OSU, including sponsoring a lecture by **Jill Pipher**. 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

Workshops at IPs

From August 2015 – July 2016, MBI helped support two workshops held at MBI partner institutions.

1. **Howard University**, April 9, 2016: Travel Grant for young researchers to attend "Precision Medicine"
2. **Virginia Commonwealth University**, May 20-22, 2016: Travel Grant for young researchers to attend "BAMM! Biology and Mathematics through Medicine"

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 2015-2016 VLP lectures were:

1. **Talitha Washington**, Truman State University, April 15-16, 2016
2. **Talitha Washington**, CSU Channel Islands, April 29, 2016

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/ .

Program Initiatives

2016-2017 Emphasis Programs

The theme for the **Autumn 2016 Emphasis Program** is *Analysis of Complex Data in Biological Systems*.

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 will explore new mathematical techniques that can be 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.

The program will consist of four workshops. Workshop 1 will focus on geometric and topological methods of data analysis. Workshop 2 will focus on mathematical methods for analyzing data sets in cancer biology. Workshop 3 will discuss the ways of linking complex data with dynamical systems models in neuroscience. Workshop 4 will be devoted to the impact of new streaming data collection techniques on population biology from the cellular, the organismal, to the ecological level, with special emphasis on the dynamics of disease spread in real time.

Organizing Committee

- **Konstantin Mischaikow**, Mathematics, Rutgers
- **Qing Nie**, Biomedical Engineering & Mathematics, Univ of California, Irvine
- **Horacio Rotstein**, Department of Math Sciences, New Jersey Institute of Tech
- **Terence Speed**, Bioinformatics, Walter & Eliza Hall Institute of Medical Research
- **Vladimir Vacic**, Computer Science, University of California, Riverside
- **Michael Waterman**, Biological Sciences, Mathematics, and Computer Science, University of Southern California

Planned Workshops for Autumn Semester 2016

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

The theme for the **Spring 2017 Emphasis Program** is *Growth and Morphogenesis.*

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.

Traditionally, mathematical modeling has focused on one particular spatial scale. However, 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:

- How to collect robust summary statistics from biological data, ranging from expression of biomarkers to the structural changes in the morphology of growing tissues?
- What is the appropriate level of model description consistent with the data available?
- 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 propose three workshops which will bring 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.

This emphasis program was inspired by the upcoming 100th anniversary of the publication of D'Arcy Thompson's book *On Growth and Form*.

Organizing Committee

- **Tomas Alarcon**, Mathematical Biology, Centre de Recerca Matemàtica
- **Philip Maini**, Wolfson Centre for Mathematical Biology, University of Oxford
- **Frederik Nijhout**, Biology, Duke University
- **Pablo Padilla**, Institute for Applied Mathematics, National Autonomous University of Mexico (UNAM)

Planned Workshops for the Spring Semester 2017

1. *The biological Challenges in Morphogenesis* (February 20-24, 2017)
2. *Modelling of Tissue Growth and Form* (March 6-10, 2017)

3. *Hybrid Multi-Scale Modelling and Validation* (March 27-31, 2017)
4. *Women Advancing Mathematical Biology: Understanding Complex Biological Systems with Mathematics* (April 24-28, 2017). Sponsored in part by Microsoft Research.