2013-2014 FULL ANNUAL REPORT

Mathematical Biosciences Institute

For DMS-0931642

TABLE OF CONTENTS PAGE

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.

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
- 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 MBI are designed to support the mission of the Institute. MBI addressed the following scientific challenges in its programming during 2013-2014:

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 bioscientist'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 bioscientists' 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 directorate for 2013-2014 included: Martin Golubitsky, Ph.D. (Principal Investigator and Institute Director); Helen Chamberlin, Ph. D. (Associate Director responsible for diversity issues); Laura Kubatko, Ph.D. (Co-Principal Investigator and Associate Director responsible for the summer education programs); Yuan Lou, Ph.D. (Associate Director responsible for the summer graduate program (stepped down December 2013)); Tony Nance, Ph.D. (Associate Director responsible for administering the postdoctoral program); Greg Rempala, Ph.D. (Associate Director responsible for providing scientific advise and liaison to the workshop organizing committees); and Andrej Rotter, Ph.D. (Associate Director responsible for providing leadership for relations between MBI and the Ohio State University Medical Center and chair of the MBI Colloquium Committee).

MBI had nine fill-time administrative staff members plus two student employees for 2013-2014. The specific positions included: one Financial and Human Resources Manager (filled by Nicola Betts, BS); one Office Administrative Associate (filled by Rebecca Martin, BS); one Program Coordinator (filled by Matthew Thompson, BS); two Program Assistants (filled by Casey Jacobs, BS and Sarah Hancock, BS); one Systems Manager (filled by Michael Siroskey, BS); one Systems Developer/Engineer (filled by Carter Schonefeld, BS); one Systems Specialist (filled by Jason Bray); and one Visual Communications Specialist (filled by April Shelton, BS).

The MBI had 18 postdoctoral fellows and researchers continuing or starting their program during 2013-2014. They were Marcio Albasini Mourao, Noelle Beckman, Josh Chang, Kimberly Fessel, Wenrui Hao, Paul Hurtado, Karly Jacobsen, Jae Kyoung Kim, Adrian Lam, Kang-Ling Liao, Wing-Cheong (Jon) Lo, Leopold Matamba Messi, Jay Newby, Michael Schwemmer, Michal Seweryn, Lucy Spardy, Marc Sturrock, and Ying (Joy) Zhou.

A. INFORMATION ON MBI PROGRAMS

1. MBI Emphasis Semester Programs

The 2013-2014 year was the first in which MBI hosted separate Emphasis Semester programs: the Autumn 2013 Emphasis Semester was on *Ecosystem Dynamics and Management* and the Spring 2014 Emphasis Semester was on Frontiers in *Imaging, Mathematics, and the Life Sciences.*

The Autumn 2013 MBI Emphasis Semester was on *Ecosystem Dynamics and Management*. A changing world raises great challenges since we need to take steps that either reduce the rate of global change or that manage resources in the face of global change. Both steps require making predictions, which requires theory. But the systems involved are truly complex, so the theory must use mathematics. Despite the long history of mathematical approaches in ecology and other environmental sciences, understanding the resilience of environmental systems in the face of global change presents substantial mathematical challenges that require novel approaches.

The mathematical issues include understanding very complex dynamical systems on appropriate time scales, with complex or stochastic forcing terms. If explicit control measures are to be designed, then issues in both control and optimal control come to the forefront. Since these are real-world problems, complex statistical issues also are present as well as computational issues. In particular, the computation and solution of partial differential equation systems (or other high dimensional systems) on irregular domains with forcing presents difficult challenges. The workshop topics highlighted both the biological and mathematical issues involved. One workshop on fundamental mathematical issues related to the study of complex systems and two workshops focused more on two broad ranging biological issues in sustainability: rapid evolution and sustainable management of living natural resources.

The Spring 2014 MBI Emphasis Semester was on *Frontiers in Imaging, Mathematics, and the Life Sciences*. This one semester program brought together researchers from mathematics, imaging technology, biology, and the life sciences to explore new ways to bridge these diverse disciplines, and to facilitate the use of mathematics for key problems in imaging, medicine, and the life sciences in general.

The hardware side of imaging has been undergoing a revolution in the past 15 years with the advent of faster, more accurate, and cheaper imaging modalities. This powerful new hardware has driven the need for corresponding new mathematical ideas that can be turned into practical algorithms and in turn implemented in software that may be used by the medical/biology community. A number of algorithms based on partial differential equations, curvature driven flows, geometry, and novel statistical techniques have already made their impact felt in image processing.

Mathematical models form the basis of biomedical computing in general and medical imaging in particular. Basing those models on data extracted from images continues to be a fundamental technique for achieving scientific progress in experimental, clinical biomedical, and behavioral research. Data and in particular imagery, acquired in a multiscale manner by a range of techniques, are central to understanding biological problems and their impacts on clinical and natural sciences. One can consider this type of data as geometrically arranged arrays of data samples measuring such diverse physical quantities as time-varying hemoglobin deoxygenation during neuronal metabolism or vector-valued measurements of water diffusion through and within tissue.

The broadening scope of imaging as a way to organize our observations of the biophysical world has led to a dramatic increase in our ability to apply novel processing techniques and to combine multiple channels of data into sophisticated and complex mathematical models including

biological systems, physiological function and dysfunction. We note that many relevant data sets from biomedical imaging, genomics and proteomics have high-dimensionality, high heterogeneity due to different data modalities (across different spatial and temporal scales, but also across different biological layers) that need to be fused, low sample size and possibly low reproducibility of per-patient data. These challenging aspects demand concepts from compressive sensing, learning and information theory, and novel algebra-geometric/topological techniques that accordingly constituted some of the key topics of this MBI program.

The workshops brought together a diverse group of researchers from mathematics, imaging, signal processing and control, medicine, biology, and the statistics communities to exchange ideas, build collaborations, and provide new directions in mathematical and biological research. Concepts and techniques from bioinformatics, genomics/proteomics, and dynamics were a part of these workshops as well.

Emphasis Semester Organizing Committees
Organizing Committee for the Autumn Semester 2013 program on *Ecosystem Dynamics and Management:*

- Jordi Bascompte (Integrative Ecology Group, Estacio n Biolo gica de Donana, Consejo Superior de Investigaciones Cientıficas, Sevilla, Spain)
- Chris Cosner (Department of Mathematics, University of Miami)
- Alan Hastings (Department of Environmental Science and Policy, University of California, Davis)
- Marc Mangel (Center for Stock Assessment Research, University of California, Santa Cruz)
- Jim Sanchirico (Department of Environmental Science and Policy, University of California, Davis)
- Mary Lou Zeeman (Department of Mathematics, Bowdoin College)

Organizing Committee for the Spring Semester 2014 program on *Frontiers in Imaging, Mathematics, and the Life Sciences*:

- Monica Hurdal (Department of Mathematics, Florida State University)
- Paul Kulesa (Developmental Biology, Stowers Institute for Medical Research)
- Mauro Maggioni (Mathematics, Duke University)
- Allen Tannenbaum (Computer Science and Applied Mathematics, Stony Brook University)
- Ross Whitaker (School of Computing, University of Utah)

Emphasis Semester Workshops
MBI hosted seven emphasis semester topic workshops in 2013-2014:

AUTUMN 2013 EMPHASIS SEMESTER WORKSHOPS

1. *Workshop 1: Sustainability and Complex Systems*
   September 16-20, 2013
   Organizers: Chris Cosner (Mathematics, University of Miami), Volker Grimm

(German Research Center for Enviromental Health), Alan Hastings (Department of Environmental Science and Policy, University of California, Davis), and Otso Ovaskainen (Biological and Environmental Sciences, University of Helsinki)

2. *Workshop 2: Rapid Evolution and Sustainability*
   October 07-11, 2013
   Organizers: Jim Cushing (Mathematics, University of Arizona), Patrick De Leenheer (Department of Mathematics, Oregon State University), Katia Koelle (Biology, Duke University), and Steve Munch (Ecology and Evolutionary Biology, University of California, Santa Cruz)
3. *Workshop 3: Sustainable Management of Living Natural Resources*
   November 04-08, 2013
   Organizers: Paul Armsworth (Ecology and Evolutionary Biology, University of Tennessee), Alan Hastings (Department of Environmental Science and Policy, University of California, Davis), and Andrew Liebhold (US Forest ServiceNorthern Research Station, Northern Research Station)

SPRING 2014 EMPHASIS SEMESTER WORKSHOPS

1. *Workshop 1: Visualizing and Modeling Cellular and SubCellular Phenomena*
   January 13-17, 2014
   Organizers: John Condeelis (Department of Anatomy & Structural Biology, Albert Einstein College of Medicine), Anna-Katerina Hadjantonakis (Developmental Biology Program, Memorial Sloan-Kettering Cancer Center), Paul Kulesa (Developmental Biology, Stowers Institute for Medical Research), and Philip Maini (Centre for Mathematical Biology, Mathematical Institute)
2. *Workshop 2: Morphogenesis, Regeneration, and the Analysis of Shape*
   February 10-14, 2014
   Organizers: Thomas Lecuit (Developmental Biology Institute of Marseille), L. Mahadevan (School of Engineering and Applied Sciences, Harvard University), and Ross Whitaker (School of Computing, University of Utah)
3. *Workshop 3: Integrating Modalities and Scales in Life Science Imaging*
   March 17-21, 2014
   Organizers: Monica Hurdal (Department of Mathematics, Florida State University), Michael Liebling (Electrical and Computer Engineering, University of California Santa Barbara), Rob MacLeod (SCI Institute and Bioengineering, University of Utah), and Kristin Swanson (Neurological Surgery, Northwestern University)
4. *Workshop 4: Analysis and Visualization of Large Collections of Imaging Data*
   April 21-24, 2014
   Organizers: Chandrajit Bajaj (Computer Science, University of Texas), Philipp Keller (Janelia Farm Research Campus, Howard Hughes Medical Institute), Mauro Maggioni (Mathematics, Duke University), and Allen Tannenbaum (Computer Science and Applied Mathematics, Stony Brook University)

2. Additional MBI Programs and Initiatives

Current Topic Workshops

MBI hosted six current topic workshops in 2013-2014:

1. *Teaching Discrete and Algebraic Mathematical Biology to Undergraduates*
   July 29 – August 2, 2013
   Organizers: Terrell Hodge (College of Arts and Sciences, Western Michigan University), Matthew Macauley (Mathematical Sciences, Clemson University), and Raina Robeva (Mathematical Sciences, Sweet Briar College)
2. *2013 Workshop for Young Researchers in Mathematical Biology*
   August 26-29, 2013
   Organizers: MBI Postdocs
3. *Mathematics Guiding Bioartificial Heart Valve Design*
   October 28-31, 2013
   Organizers: Suncica (Sunny) Canic (Mathematics, University of Houston—Downtown), Boyce Griffith (Medicine, New York University School of Medicine), Arash Kheradvar (Biomedical Engineering, University of California Irvine), and Stephen Little (Cardiovascular Imaging Section, Department of Cardiology, Houston Methodist Hospital)
4. *From Within Host Dynamics to the Epidemiology of Infectious Disease*
   April 07-11, 2014
   Organizers: Steve Cantrell (Mathematics, University of Miami), Mary Galinski (Medicine, Emory University School of Medicine, Division of Infectious Diseases), and Juan Gutierrez (Mathematics, Institute of Bioinformatics, University of Georgia)
5. *Molecular to Systems Physiology*
   May 05-09, 2014
   Organizers: Daniel Beard (Department of Physiology, Medical College of Wisconsin), Laura Ellwein (Mathematics, Virginia Commonwealth University), and Mette Olufsen (Department of Mathematics, North Carolina State University)
6. *2014 ICIAM Scientific Workshop*
   May 15-16, 2014
   Organizers: Jose Cuminato (Applied Mathematics and Statistics, University of Sao Paulo), Maria J. Esteban (CEREMADE, CNRS & University Paris-Dauphine), Alistair Fitt (Senior Management Team, Oxford Brookes University), Barbara Keyfitz (Department of Mathematics, The Ohio State University), Taketomo Mitsui (Professor Emeritus, Nagoya University), and Mario Primicerio (Mathematics, Università degli Studi di Firenze)
   ICIAM was hosted by MBI, with funding provided by the Ohio State University's Mathematics Research Institute (MRI) and by the Institute for Mathematics and its Applications (IMA).

Education

MBI hosted two education programs in 2013-2014:

1. *2014 Summer Undergraduate Program*

May 20 - August 16, 2013
The program consisted of three parts:

a. *Two-Week Program* (June 2-13, 2014): Tutorials, computer labs, and short-term team efforts designed to introduce students to a variety of topics in mathematical biology.
b. *REU Program* (June 16 – August 8, 2014): An 8 week 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, Howard University, Indiana University – Purdue University Indianapolis, University of Notre Dame, The Ohio State University, University of Pittsburgh, and the Virginia Bioinformatics Institute at Virginia Tech.
c. *Capstone Conference* (August 11-15, 2014): A student centered conference featuring talks and posters by students doing research in mathematical biology, keynotes by prominent mathematical biologists, a graduate studies recruitment fair, and other special features.

2. *Joint 2014 MBI-NIMBioS-CAMBAM Summer Graduate Program: Rythms and Oscillations*
July 7-18, 2014
Organizers: Daniel Forger (Mathematics, University of Michigan) and Paul Francois (Department of Physics, McGill University)
This summer school focused on the theory, mathematical modeling and experimental study of biological rhythms. The workshop included a boot camp to introduce the basic mathematical tools and techniques used in studying biological rhythms. In depth explorations of specific problems were presented and students worked in small groups on projects, which they presented at the end of the two week workshop.

Mathematics of Planet Earth (MPE 2013)

MPE 2013 was an initiative of mathematical sciences organizations around the world designed to showcase the ways in which the mathematical sciences can be useful in tackling our world's problems. This initiative led to plans for many events to take place in 2013, including more than 10 long term programs at institutes around the world, more than 50 workshops, many invited speakers and special sessions at societal meetings, numerous public lectures (including the MPE 2013 Simons Public Lecture Series http://mpe2013.org/public-lectures/mpe2013-simons-public-lecture-series/), the development of educational materials, art exhibits, a daily blog and an international prize competition to create innovative modules for display and use and which can be widely disseminated and exhibited.

MBI is a partner organization of MPE 2013 and planned a semester-long program plus a workshop in Mathematical Demography designed around the theme of MPE 2013:

- The Keyfitz Centennial Symposium on Mathematical Demography (June 24-28, 2013)
- The Ecosystem Dynamics and Management semester program
- Workshop 1: Sustainability and Complex Systems (September 16-20, 2013)
- Workshop 2: Rapid Evolution and Sustainability (October 7-11, 2013)

- Workshop 3: Sustainable Management of Living Natural Resources (November 4-8, 2013)

The successful year-long MPE 2013 initiative has continued beyond 2013. It is now simply called MPE and its permanent website is http://mpe.dimacs.rutgers.edu.

Courses

This year MBI continued hosting courses aimed at exposing and educating the post-docs in active areas of mathematical biology. The course lectures were live video streamed.

MBI hosted two education programs in 2013-2014:

1. *Fall 2013 Course: Introduction to genomic methods to answer biological questions*
   September 06, 2013 - October 25, 2013
   Helen Chamberlin (Molecular Genetics, The Ohio State University)
   Abstract: Recent innovations have allowed researchers and clinicians to determine the complete sequence of DNA and RNA samples from individuals and even populations rapidly and cheaply. These methods are revolutionizing the types of biological questions that experimentalists can ask, and the types of datasets available for computational analysis. This course will provide an introduction to these methods and their biological applications. Course participants will use class discussion and readings from the research literature to identify how laboratory researchers apply these methods, and to recognize the strengths and the limitations of genomic approaches.
2. *Semester Course: Statistical Learning*
   January 21, 2014 - April 15, 2014
   Greg Rempala (MBI and College of Public Health, The Ohio State University)
   Abstract: The course covers basic concepts of modern statistical learning theory. The theory itself is born out of the challenge of understanding vast amounts of data routinely collected in modern science and has led to the development of new tools in the field of statistics, as well as has spawned new computer-assisted areas of research, such as data mining, machine learning, and bioinformatics. Many of these tools have common underpinnings but are often described with different terminology. This course attempts to collect some main ideas of statistical learning into a common conceptual framework appropriate for the audience with mathematical background.

Visiting Lecture Program

MBI developed the Visiting Lecturer Program (VLP) in 2009. The program sponsors visits of mathematical biologists to institutions that have large numbers of undergraduate students who are members of groups that are underrepresented 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. In addition to delivering a lecture on mathematical biology that is accessible to an undergraduate audience, the lecturers will meet with individual students and with groups of interested faculty and students to further this purpose.

In 2013-2014, MBI had two VLPs:

1. Talitha Washington (Mathematics, Howard University)
   May 2, 2014 lecture at University of Hawaii at Manoa
   Increasing the Diversity of Women in the Sciences: Advantages of and Pathways to the Ph.D.
2. Fabio Milner (Mathematics, Arizona State University)
   November 22, 2013 lecture at Prairie View A&M University
   The Mathematics of Sex, Marriage and Disease
   Abstract: A historical perspective of demographic models will be presented, from the simplest, unstructured, exponential growth models, to state-of-the-art, age- and sex structured ones with logistic growth. The marriage problem will be described and examples using real-life data will be used to apply models to population forecasting. Finally, some examples of application of these models to epidemic forecasting will be shown, to childhood and to sexually transmitted diseases.

Public Lecture Series

MBI continued to be instrumental in the Science Sundays Public Lecture Series sponsored by the College of Arts and Sciences at OSU. Science Sundays lectures are held monthly during the academic year 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.

In 2013-2014, MBI sponsored four public lectures:

1. *The Great Animal Orchestra*
   Bernie Krause (Founder, Wild Sanctuary)
   October 13, 2013
2. *Sickle Cell Anemia: Physics and Physiology of a Molecular Disease*
   M. Mahadevan (Applied Mathematics, Organismic and Evolutionary Biology and Physics, Harvard)
   February 9, 2014
3. *Mathematics and Human Physiology*
   Mike Reed (Mathematics, Duke University)
   March 2, 2014
4. *Falling Paper and Insect Flight*
   Jane Wang (Mechanical and Aerospace Engineering and Physics, Cornell)
   April 13, 2014

MBI Colloquium Program

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 MBI post-docs. The talks are live video streamed.

2013-2014 Colloquia:

1. *Stochastic Wilson-Cowan equations for networks of excitatory and inhibitory neurons*
   Jack Cowan (Mathematics, University of Chicago)

September 09, 2013 3:00 - 3:50PM

2. *Neurally and ocularly informed graph-based models for searching 3D environments*
   Paul Sajda (Biomedical Engineering and Radiology, Columbia University)
   September 23, 2013 3:00 - 3:50PM
3. *Unraveling the mysteries of Soundscapes*
   Bernie Krause (Wild Sanctuary)
   October 14, 2013 3:00 - 3:50PM
4. *Molecular-motor based transport: how does it function, and what can theoretical modeling contribute to understanding it?*
   Steven Gross (Developmental and Cell Biology, University of California, Irvine)
   November 18, 2013 3:00 - 3:50PM
5. *The Interplay of Conservation and Correlation in Enzyme Stability*
   Thomas Magliery (Chemistry, The Ohio State University)
   November 25, 2013 3:00 - 3:50PM
6. *Modeling dominant protein interactions that influence the pathogenesis of protein folding diseases*
   Santiago Schnell (Department of Molecular & Integrative Biology, Department of Computational Medicine & Bioinformatics, Brehm Center for Diabetes Research, University of Michigan)
   January 27, 2014 3:00 - 3:50PM
7. *Computability, Gödel's Incompleteness Theorem, and an Inherent limit on the Predictability of Evolution*
   Troy Day (Mathematics and Statistics, Queen's University)
   February 03, 2014 3:00 - 3:50PM
8. *Models, Mechanisms, and Bifurcations of Collective Animal Behavior*
   Naomi Leonard (Mechanical and Aerospace Engineering, Princeton University)
   February 24, 2014 3:00 - 3:50PM
9. *Understanding the Causes and Cures of Type 2 Diabetes with a Mathematical Model*
   Arthur Sherman (National Institutes of Health)
   March 03, 2014 3:00 - 3:50PM
10. *In Vivo Imaging of the Developing Mouse Brain: From Morphology to Molecules*
    Daniel Turnbull (Radiology and Skirball Institute, New York University School of Medicine)
    March 17, 2014 3:00 - 3:45PM
11. *The Fate of the Global Carbon Sink*
    Stephen Pacala (Ecology and Ecolutionary Biology, Princeton University)
    March 24, 2014 3:00 - 3:50PM
12. *Phase I trials in melanoma: Optimizing order and timing of combination therapy*
    Alexander Anderson (Integrated Mathematical Oncology, H. Lee Moffitt Cancer Center & Research Institute)
    April 14, 2014 3:00 - 3:50PM
13. *Recent Advances in 3D Blood flow Simulation: From Parameter Estimation Methods to Clinical Applications*
    Alberto Figueroa (Department of Biomedical Engineering, King's College)

May 05, 2014 4:00 - 5:00PM

Early Career Awards
Early Career Awards are aimed at non-tenured scientists who currently have continuing employment and who hold a doctorate in any of the mathematical, statistical and computational sciences, or in any of the biological, medical and related sciences. Awardees engage in an integrated program of tutorials and workshops tied to the scientific theme and are expected to interact with local and visiting researchers.

2013-2014 Early Career Awardees:

1. Leah Johnson (Department of Ecology and Evolution, University of Chicago)
   August 2013 - December 2013
2. Maria Leite (Mathematics and Statistics, University of Toledo)
   August 2013 - December 2013
3. Remus Osan (Mathematics and Statistics, Georgia State University)
   January 2014 - May 2014
4. Hao Wang (Department of Mathematics and Statistics, University of Alberta)
   September 2013 - December 2013

Long Term Visitor Seminar
With the number and scientific breadth of MBI's Long Term Visitors and Early Career Awardees, MBI features seminar talks by Long Term Visitors. These talks are held during non-workshop weeks at MBI.

2013-2014 Long Term Visitor Seminar Speakers:

1. *Simple food web modules that combine population dynamics with evolutionary trait dynamics*
   Vlastimil Krivan (Biology Center, Czech Academy of Sciences (AVv CR))
   September 10, 2013 10:20 - 11:15AM
2. *Genetic architecture and the evolution of local adaptation and differentiation with gene flow*
   Reinhard Burger (Department of Mathematics, University of Vienna)
   September 24, 2013 10:20 - 11:15AM
3. *Inference for Mechanistic Models: Case Studies in Ecology*
   Leah Johnson (Department of Ecology and Evolution, University of Chicago)
   October 01, 2013 10:20 - 11:20AM
4. *Two Little Known Theorems of Sam Karlin: Their implications for biological invasions, genetic system evolution, cultural evolution, and ideal free distributions in ecology*
   Lee Altenberg (Ronin Institute, Ronin Institute)
   October 15, 2013 10:20 - 11:15AM
5. *Modeling cholera dynamics*
   Jin Wang (Department of Mathematics and Statistics, Old Dominion University)
   October 22, 2013 10:20 - 11:15AM
6. *Integral Tracking for Population Management*

Richard Rebarber (Mathematics, University of Nebraska)
November 12, 2013 10:20 - 11:15AM

7. *Modeling population dynamics driven by external factors*
   Maria Leite (Mathematics and Statistics, University of Toledo)
   November 19, 2013 10:20 - 11:15AM
8. *Study the "Strict Homeostasis" Assumption in Ecological Stoichiometry via Bifurcations*
   Hao Wang (Department of Mathematics and Statistics, University of Alberta)
   December 03, 2013 10:20 - 11:15AM
9. *Modeling and Analyzing Cortical Folding Patterns of the Human Brain in Development, Aging, and Disease*
   Monica Hurdal (Department of Mathematics, Florida State University)
   March 11, 2014 9:10 - 10:00AM
10. *Effects of synaptic connectivity inhomogeneities on dynamics of wave propagation in neural tissue*
    Remus Osan (Mathematics and Statistics, Georgia State University)
    May 01, 2014 10:20 - 11:15AM

Conference Awards

The MBI Conference Award is a program that started as a diversity initiative in which untenured junior faculty, postdocs, and graduate students are awarded a fully funded trip to attend a MBI workshop of the winner's choice. MBI works with event organizers to set up an evaluation procedure to identify winners at national meetings, including the SACNAS Modern Math Meeting, SIDIM, and the Blackwell Memorial Conference. MBI intends to expand this program by working in conjunction with AWM, Blackwell-Tapia organizers, and others.

In 2013-2014, MBI awarded three Conference Awards:

1. Alicia Machuca
   Department of Mathematics, University of Texas at Arlington
   An Exact Solution Formula for the Kadomtsev-Petviashvili II Equation
   SACNAS National Conference (October, 2013)
2. Amanda Parra
   Mathematics, Texas Tech University
   Determination of carbon nanotube uptake, translocation, and bioaccumulation in corn grown in soil
   SACNAS National Conference (October, 2013)
3. Aisha Najera Chesler
   Mathematics, Claremont Graduate University
   Heart Rate and EEG modeling during labor: predicting fetal distress
   Joint Mathematics Meeting, Baltimore, MD (January, 2014)

MBI Initiatives for 2014-2015

The theme for the 2014-2015 emphasis year is *Cancer and Its Environment*. Cancer is one of the world's biggest killers. Cancer is initiated from cells with specific genetic mutations that cause

them to lose control of proliferation. This loss of proliferative control, whilst necessary, is not sufficient to cause cancer; subsequent mutations and selection need to occur. Cancer is an evolutionary disease, where rounds of mutation and selection will drive the emergence of a tumor. The selection pressures that a growing tumor encounters are manifold but can largely be classified as microenvironmental. The tumor microenvironment consists of the extracellular matrix, growth promoting and inhibiting factors, nutrients (including oxygen and glucose), chemokines, and importantly, other cell types including (but not limited to) fibroblasts, immune cells, endothelial cells and normal epithelial cells. In order for selection to operate properly there needs to be variation in the tumor population -- tumors are known to be genetically extremely heterogeneous. This genetic heterogeneity produces phenotypic heterogeneity in which individual tumor cells can have distinct phenotypic behaviors within the same tumor.

As the tumor mass grows, so does the heterogeneity; eventually the mass becomes too large to be supported by nutrient diffusion alone, so some subset of the tumor population then becomes hypoxic. This hypoxia will eventually give way to cell death if nutrient levels continue to fall but the tumor has two ways to combat this problem. First it can begin to utilize a different nutrient source (e.g. glucose) by altering its metabolism and second it can initiate the process of angiogenesis from nearby vessels. The process of recruiting and growing a new vasculature, once fully realized, gives the tumor an almost limitless nutrient source and also a highway to other parts of the human body. Metastases are cells that successfully break away from the primary tumor and initiate new tumors at secondary sites. There can be many of these metastatic cancers at many different sites in the body and ultimately, for most patients, it is these cancers that cause death.

There are hundreds of types of cancer, classified by the tissue from which they arise and by the type of cells involved. For example, leukemia is a cancer of white blood cells, carcinoma is a cancer originating from epithelial cells and glioma is cancer of the brain. There are also many ways to treat cancer, most of which start with surgery and end with chemotherapy and/or radiotherapy. In recent years we have seen the emergence of immunotherapies and molecularly targeted therapies. Immunotherapies exploit the immune system by either enriching or aiding its ability to attack the cancer. Molecularly targeted therapies exploit the fact that specific mutations are present in a large proportion of the cancer cells and block the activity of these mutations. Both of these new therapies have had differing degrees of success but, as in most treatments, failure is ultimately caused by the emergence of a resistant tumor population that tends to be more aggressive and less easy to treat.

This brief overview illustrates the complex interactions at the molecular, cellular and tissue levels involved in the emergence and development of cancer, and emphasizes the need for mathematical models that synthesize a framework for understanding the existing phenomena and that make testable predictions as to how interventions will influence the outcome.

Organizing Committee for 2014-2015

- Alexander Anderson, Integrated Mathematical Oncology, H. Lee Moffitt Cancer Center & Research Institute
- Rick Durrett, Department of Mathematics, Duke University

- Mariam Eljanne, Physical Sciences-Oncology, National Institutes of Health (NIH)
- Avner Friedman, Department of Mathematics, The Ohio State University
- Kirk Jordan, IBM Strategic Growth Initiatives, IBM Corporation
- John Lowengrub, Mathematics, University of California, Irvine
- Guido Marcucci, Comprehensive Cancer Center, The Ohio State University
- Hans Othmer, School of Mathematics, University of Minnesota
- Vito Quaranta, Vanderbilt Ingram Cancer Biology Center, Vanderbilt University

Events Planned in 2014-2015

1. *2014 Workshop for Young Researchers in Mathematical Biology*
   August 25 - 28, 2014
2. *Workshop 1: Ecology and Evolution of Cancer*
   September 15 - 19, 2014
3. *Boot Camp: How to Simulate and Analyze Your Cancer Models with COPASI* September 29 - October 1, 2014
4. *Workshop 2: Metastasis and Angiogenesis*
   October 13 - 17, 2014
5. *CTW: Axonal Transport and Neuronal Mechanics*
   November 3 - 7, 2014
6. *Workshop 3: Cancer and the Immune System*
   November 17 - 21, 2014
7. *Workshop 4: Tumor Heterogeneity and the Microenvironment*
   February 2 - 6, 2015
8. *Workshop 5: Treatment, Clinical Trials, Resistance*
   February 16 - 20, 2015
9. *Workshop 6: Targeting Cancer Cell Proliferation and Metabolism Networks*
   March 23 - 27, 2015
10. *Workshop 7: Stem Cells, Development, and Cancer*
    April 13 - 17, 2015
11. *CTW: Evolutionary Game Theory*
    April 27 - May 01, 2015

Web Initiatives

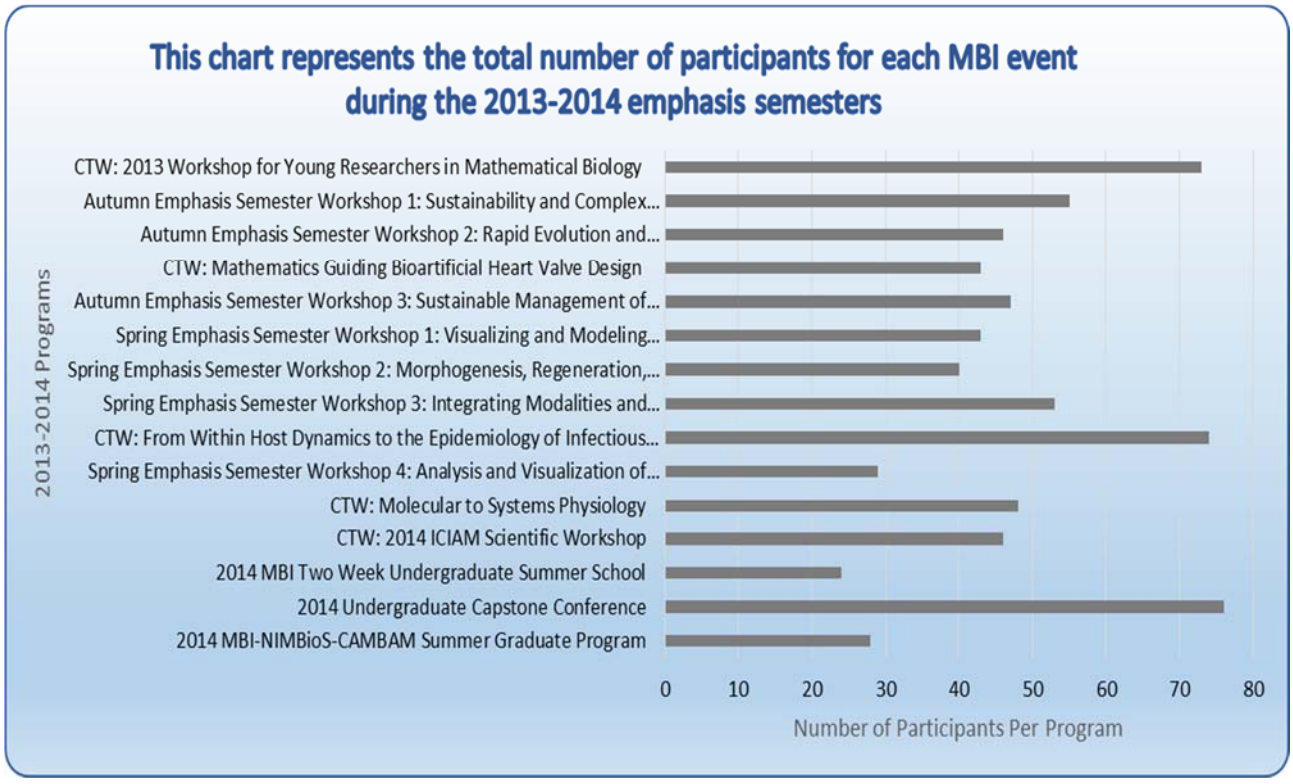
- MBI website redesign
- Online workshop tutorials
- Distance colloquia and seminars

3. Participant Data

725 participants took part in MBI's 2013-2014 current topic workshops and emphasis semester programs.

Participants who received direct funding (travel, meal per diem, and stipend) at MBI workshops are reported in a supplemental spreadsheet which details their professional affiliation, designation and the amount of financial support paid to each participant per event.

This chart shows the total number of participants per event in 2013-2014:

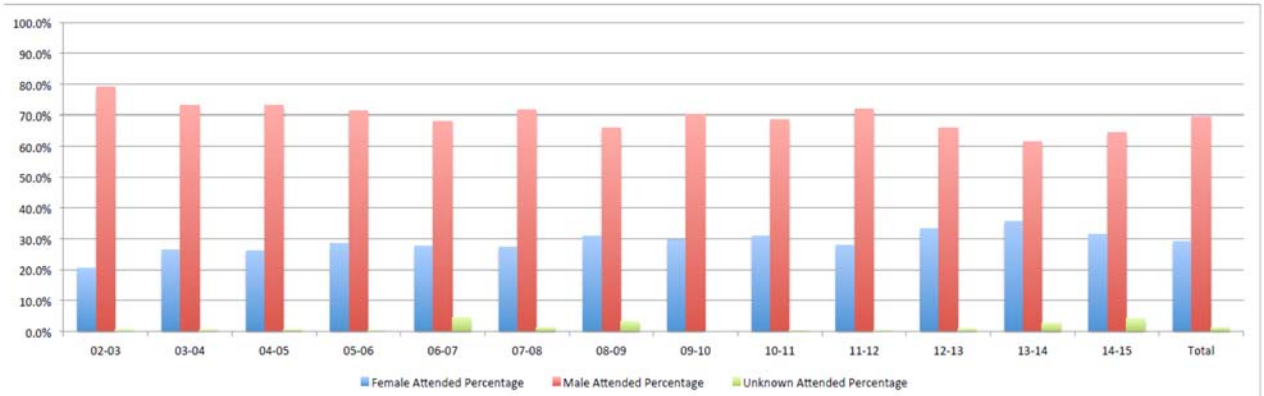


Gender Data

A demographic goal for the current grant was to increase the percentages of women who were supported participants and speakers. In 2010 the MBI Board of Trustees passed a rule requiring all MBI workshops to have at least 20% female speakers and at least 20% female invited participants. This rule helped MBI to accomplish this goal.

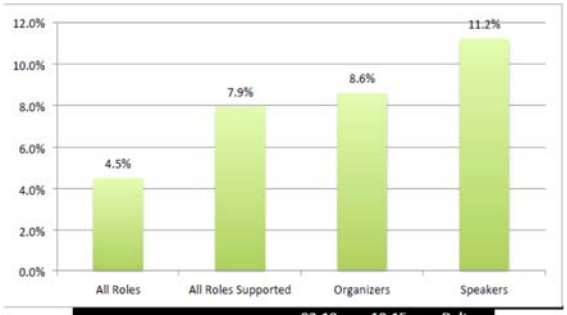
To provide as accurate a picture as possible we began with the reported gender data, which had a large number of non-responses, and we created a shadow database with inferred data. The missing data was identified in two ways: entering the gender of people we knew and web searches for the remainder. The inferred data leads to the results in the following tables. Note that the percentage of women speakers has increased by over 11 percentage points to 26.2% and the percentage of supported women has increased by 4.5% to 31.7%. See the following tables for a yearly breakdown.

Yearly Breakdown of Inferred Gender for All Atteded Particpants



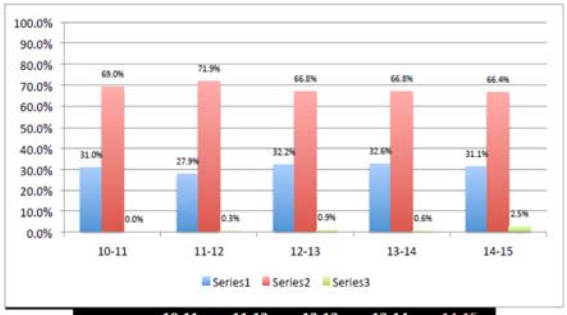
	02-03	03-04	04-05	05-06	06-07	07-08	08-09	09-10	10-11	11-12	12-13	13-14	14-15	Total
Female Attended Percentage	20.6%	26.4%	26.3%	28.4%	27.6%	27.2%	31.0%	29.7%	31.0%	27.8%	33.2%	35.7%	31.4%	29.0%
Male Attended Percentage	79.0%	73.1%	73.1%	71.5%	68.1%	71.6%	65.9%	70.3%	68.8%	72.0%	66.0%	61.7%	64.6%	69.7%
Unknown Attended Percentage	0.4%	0.5%	0.7%	0.2%	4.3%	1.2%	3.1%	0.0%	0.3%	0.2%	0.8%	2.6%	4.0%	1.3%
Female Attended	102	167	198	179	236	177	168	198	228	250	291	259	55	2508
Male Attended	391	463	551	451	582	466	357	468	506	647	578	447	113	6020
Unknown Attended	2	3	5	1	37	8	17	0	2	2	7	19	7	110

Percentage of Females (Inferred) on Previous vs Current Grant



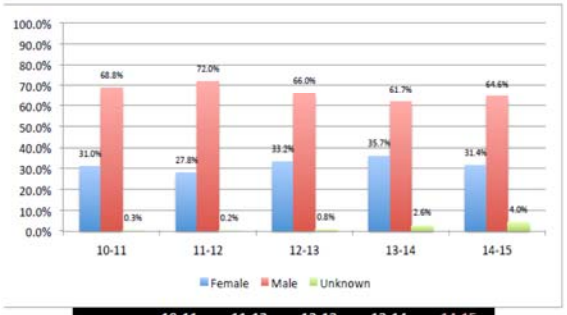
	02-10	10-15	Delta
All Roles	27.3%	31.8%	4.5%
All Roles Supported	22.9%	30.8%	7.9%
Organizers	15.0%	23.6%	8.6%
Speakers	15.0%	26.2%	11.2%

2010-2015 Supported Attended Inferred Gender



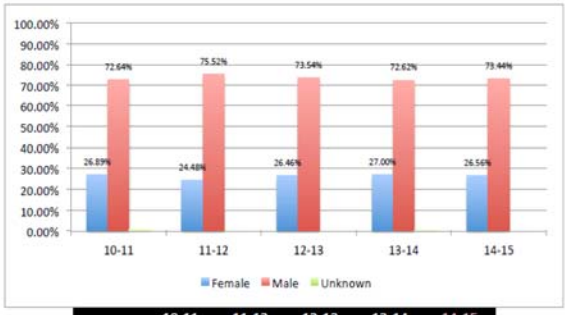
	10-11	11-12	12-13	13-14	14-15
Female	171	217	246	174	38
Male	381	560	510	356	81
Unknown	0	2	7	3	3

2010-2015 Attended Inferred Gender



	10-11	11-12	12-13	13-14	14-15
Female	228	250	291	259	55
Male	506	647	578	447	113
Unknown	2	2	7	19	7

2010-2015 Attended Speaker Inferred Gender



	10-11	11-12	12-13	13-14	14-15
Female	57	59	59	71	17
Male	154	182	164	191	47
Unknown	0	0	0	0	0

Diversity Data
MBI's diversity data is self-reported and incomplete with nearly 43% of participants either declining to supply this information or not answering the question. With our new database MBI is now better able to keep track of reported data. Of the 1954 participants who responded (as opposed to the 1471 who did not) in the past four plus years, 203 are African American, Hispanic, or Native American; thus 10.4% of those reporting are from underrepresented groups.

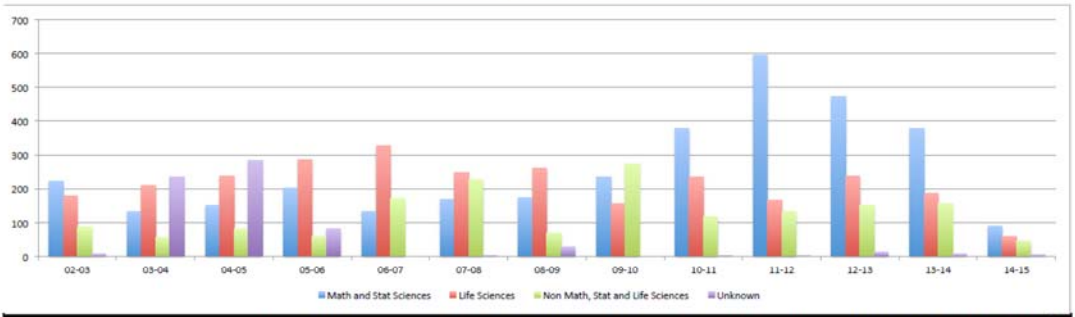
Geographic Data
MBI attracts researchers from around the country and indeed around the world to its workshops. In the past four plus years researchers from at least 47 of the 50 states have attended MBI programs. Of course, the state with the largest percentage of attendees is Ohio (and indeed most of these participants are from Ohio State); but that percentage is just 15.7% of the total USA attendees.

Internationally, MBI has attracted participants from at least 47 countries. By far the largest numbers are from the United Kingdom (24.1%) and Canada (21.0%). So far, the percentage of international participants during this grant has been at least 21.2%.

Mathematical Scientists versus Other Scientists
A major thrust of the current MBI grant was to increase the number of bio-to-math programs that MBI hosted and to increase the number of math sciences researchers who visit MBI. To facilitate this, we planned to increase the number of math scientists by increasing the number of CTW from 4 to 6 a year, with the additional workshops aimed mainly at bio-to-math. In this way we planned to keep the number of life scientists visiting MBI at an approximately constant level. The data shows that so far we have more or less accomplished this goal.

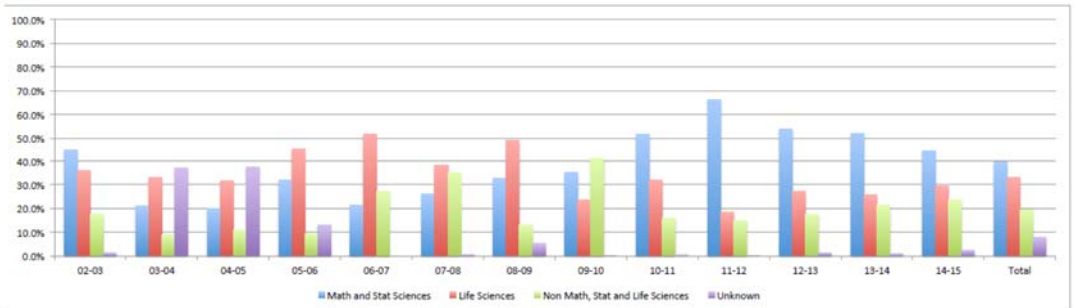
For example, for the current grant, the following tables show that the percentage of math scientist MBI participants is at 55.8% (43.6% for speakers), whereas the corresponding number for the previous eight years was 27.5% (16.4% for speakers).

Yearly Breakdown of Attended Inferred Fields by Number



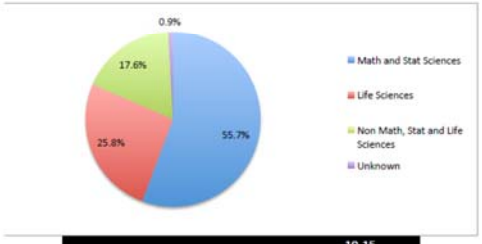
	02-03	03-04	04-05	05-06	06-07	07-08	08-09	09-10	10-11	11-12	12-13	13-14	14-15	Total
Math and Stat Sciences	223	134	150	202	134	170	174	235	379	596	473	377	90	3337
Life Sciences	178	209	239	287	326	249	262	156	236	166	238	186	59	2791
Non Math, Stat and Life Sciences	87	56	82	60	172	228	70	274	118	134	152	155	47	1635
Unknown	7	234	283	82	0	4	28	1	3	2	13	7	5	669

Yearly Breakdown of Attended Inferred Fields by Percentage



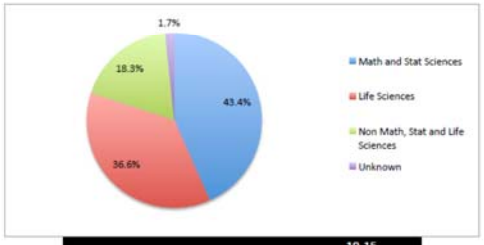
	02-03	03-04	04-05	05-06	06-07	07-08	08-09	09-10	10-11	11-12	12-13	13-14	14-15	Total
Math and Stat Sciences	45.1%	21.2%	19.9%	32.0%	21.2%	26.1%	32.6%	35.3%	51.5%	66.4%	54.0%	52.0%	44.8%	39.6%
Life Sciences	36.0%	33.0%	31.7%	45.5%	51.6%	38.2%	49.1%	23.4%	32.1%	18.5%	27.2%	25.7%	29.4%	33.1%
Non Math, Stat and Life Sciences	17.6%	8.8%	10.9%	9.5%	27.2%	35.0%	13.1%	41.1%	16.0%	14.9%	17.4%	21.4%	23.4%	19.4%
Unknown	1.4%	37.0%	37.5%	13.0%	0.0%	0.6%	5.2%	0.2%	0.4%	0.2%	1.5%	1.0%	2.5%	7.9%

2010-2015 Attended Inferred Fields Total



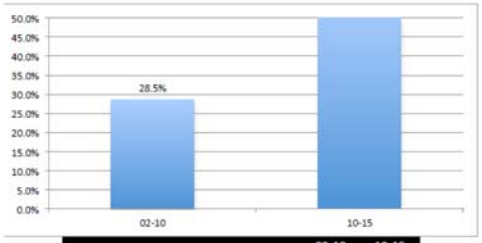
	10-15	
Math and Stat Sciences	1915	55.7%
Life Sciences	885	25.8%
Non Math, Stat and Life Sciences	606	17.6%
Unknown	30	0.9%

2010-2015 Speaker Inferred Fields Total



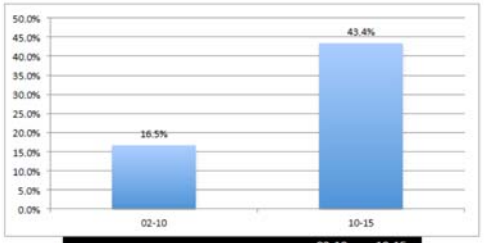
	10-15	
Math and Stat Sciences	438	43.4%
Life Sciences	370	36.6%
Non Math, Stat and Life Sciences	185	18.3%
Unknown	17	1.7%

Increase in Math Particpation for All Supported Particpants



	02-10	10-15
Math and Stat Sciences	28.5%	55.7%
Life Sciences	38.2%	25.8%
Non Math, Stat and Life Sciences	20.6%	17.6%
Unknown	12.8%	0.9%

Increase in Math Particpation for Speakers



	02-10	10-15
Math and Stat Sciences	16.5%	43.4%
Life Sciences	58.9%	36.6%
Non Math, Stat and Life Sciences	22.8%	18.3%
Unknown	1.8%	1.7%

4. Visitors

Attracting long-term visitors (LTV) to MBI is one of the main purposes in hosting emphasis programs. The LTV, along with postdoctoral fellows, create a stimulating research atmosphere that continues between workshops. During the past few years, MBI has attempted to add to the numbers of LTV in several ways. First, from the beginning of discussions with emphasis program organizers, MBI makes it clear that part of their responsibility is to arrange for long-term visits for themselves and for others. Second, MBI experimented with a math (rather than a bio) centered emphasis program for 2011-2012 (*Stochastics in Biological Systems*); indeed this program did enlarge the number of LTV. Third, MBI created the Early Career Awards program (ECA), which enables young tenure-track researchers to spend three to nine months at MBI in coordination with emphasis programs. This program began in earnest in 2010 with the beginning of this grant (DMS-0931642).

2013-2014 Early Career Awardees

1. Leah Johnson
   Department of Ecology and Evolution, University of Chicago
   August 2013 - December 2013
2. Maria Leite
   Mathematics and Statistics, University of Toledo
   August 2013 - December 2013
3. Remus Osan
   Mathematics and Statistics, Georgia State University
   January 2014 - May 2014
4. Hao Wang
   Department of Mathematics and Statistics, University of Alberta
   September 2013 - December 2013

2013-2014 Long-Term Visitors

1. Komi Afassinou
   School of Mathematics, Statistic and Computer Science, University of KwaZulu-Natal
   August 2013 - September 2013
2. Lee Altenberg
   Ronin Institute, Ronin Institute
   September 2013 - November 2013
3. Reinhard Burger
   Department of Mathematics, University of Vienna
   September 2013 - October 2013
4. Steve Cantrell
   Mathematics, University of Miami
   September 2013 - October 2013
5. Obiora Collins

School of Mathematics, Statistics and Computer Science, University of KwaZulu-Natal
August 2013 - September 2013

6. Chris Cosner
   Department of Mathematics, University of Miami
   September 2013 - October 2013
7. Bruce Gluckman
   Engineering Sciences and Mechanics, Pennsylvania State University
   March 2014 - May 2014
8. Monica Hurdal
   Department of Mathematics, Florida State University
   February 2014 - March 2014
9. Leah Johnson
   Department of Ecology and Evolution, University of Chicago
   August 2013 - December 2013
10. Eddy Kimba Phongi
    School of Mathematics, Computer science and Statistic, University of KwaZulu-Natal
    August 2013 - September 2013
11. Vlastimil Krivan
    Biology Center, Czech Academy of Sciences (AVv CR)
    August 2013 - November 2013
12. Martin Krupa
    Paris-Rocquencourt Centre, Radboud Universiteit
    April 2014
13. Maria Leite
    Mathematics and Statistics, University of Toledo
    August 2013 - December 2013
14. Jinhuo Lou
    Department of Mathematics, Shanghai University
    January 2013 - January 2014
15. Farai Nyabadza
    Division of Mathematics, Stellenbosch University
    April 2014 - July 2014
16. Remus Osan
    Mathematics and Statistics, Georgia State University
    January 2014 - May 2014
17. Patrick Phepa
    Mathematics, Statistics and Computer Science, University of KwaZulu-Natal
    April 2014
18. Richard Rebarber
    Mathematics, University of Nebraska
    October 2013 - November 2013
19. Bob Rink
    Mathematical Analysis, Vrije Universiteit

February 2014

20. Anando Sen
    Department of Biomedical Engineering, University of Houston
    March 2014
21. Nourridine Siewe
    Mathematics, Howard University
    January 2014
22. Hao Wang
    Department of Mathematics and Statistics, University of Alberta
    September 2013 - December 2013
23. Jin Wang
    Department of Mathematics and Statistics, Old Dominion University
    September 2013 - October 2013

B. MBI POSTDOCTORAL EDUCATION

The MBI had 18 postdoctoral fellows and researchers continuing or starting their program during 2013-2014. They were Noelle Beckman, Josh Chang, Kimberly Fessel, Wenrui Hao, Paul Hurtado, Karly Jacobsen, Jae Kyoung Kim, Adrian Lam, Kang-Ling Liao, Wing-Cheong (Jon) Lo, Leopold Matamba Messi, Marcio Albasini Mourao, Jay Newby, Michael Schwemmer, Michal Seweryn, Lucy Spardy, Marc Sturrock, and Ying (Joy) Zhou.

Postdoctoral candidates apply to MBI through mathjobs.org or by direct application (now rare). MBI received 177 applicants in 2013-2014 and made seven hires.

Postdoctoral Fellows Duties and Oppurtunities

- Postdoc Seminar: Each post-doc is asked to give one 50-minute colloquium level talk each year. They usually receive feedback from these talks from the Directors. The MBI postdoctoral fellows organize the weekly series (during weeks when no other MBI event is planned).
- Postdoc Mentoring: Each MBI postdoc is asked to choose two designated scientific mentors: one from the mathematical sciences and one from the life sciences. Designated mentors can be researchers at Ohio State or at other MBI Institute Partners. When the designated mentor resides outside of Columbus, MBI provides travel funds for the postdoc to visit with the mentor as often as is needed. Usually these trips are for one-week and occur 3-4 times annually.
- Employment after Leaving MBI: Postdoc job searches are usually mentored by the postdoc's scientific mentors and by the Directors and Senior Scientific Advisor. Their searches have been successful at a wide variety of institutions.
- MBI Courses for Postdoctoral Fellows: This is a new program aimed at increasing the skill sets of MBI postdocs while they are in residence at MBI. These courses are video-streamed.
- Professional Development Seminar: MBI Senior Scientific Advisor, Mike Reed, organizes seminars for the MBI Postdoctoral Fellows on professional issues, such as how to prepare

a two-minute elevator talk, how to prepare a job talk, how to prepare a grant proposal, pointers on teaching, the need for a professional website, etc. The fellows critique each other's performances in a friendly atmosphere.

- Postdoc Teaching: MBI has a cooperative program with the Mathematics Department that permits the MBI postdoctoral fellows to gain this teaching experience. Post-docs who wish to teach in a department other than Mathematics are handled on a case-by-case basis.
- Postdocs and Workshop Final Reports: Each MBI post-doc is asked to participate in the writing of final reports for two MBI workshops.
- Grant Applications and MBI Postdoctoral Fellows: MBI postdoctoral fellows are encouraged to submit at least one grant proposal to either NSF or NIH during their stay at MBI.
- Postdoc Annual Reviews: Each postdoc is formally evaluated annually. The postdocs are asked to submit a form that details their work during the past year and asks them to describe their research directions for the next year. The Directorate reads these forms and two directors meet with each postdoc to discuss his or her progress and their goals for the next year.

1. Bios for MBI Postdoctoral Fellows

Noelle G. Beckman
Ecology, Evolution, Behavior, University of Minnesota
Noelle investigates the roles of plant-animal, plant-microbe, and plant-plant interactions in limiting populations and maintaining diversity in temperate and tropical ecosystems. Using statistical models to analyze experimental and observational data, she can quantify the relationship between plant attributes and plant interactions with their environment to enable prediction for unstudied species, gain insight into the mechanisms for species coexistence, and understand ecosystem responses to change. Using mathematical and computational approaches, Noelle is investigating processes occurring over multiple spatial and temporal scales in order to address questions of species coexistence. She is also working to develop stochastic spatial models and analytical approximations to examine the interacting effects of seed dispersal and natural enemy attack on plant spatial patterns and the influence of these local interactions on plant diversity.

Josh Chang
Biomathematics, University of California, Los Angeles
Josh is excited about a variety of fields in the mathematical and physical sciences including but not limited to inverse problems, PDEs, homogenization theory, statistical physics, computer vision, and stochastic processes. His prior research has focused on regularization techniques applicable to inverse problems and computer vision. He has also worked on modeling of neurophysiology using reaction-diffusion equations. Aside from mathematical neuroscience, he is particularly curious about cancer growth, quorum sensing, pattern formation, scar formation, and models of nutrient delivery in vascular networks. Somewhat tangentially, he also likes to explore methods for transit modeling and other practical problems related to civil engineering.

Kimberly Fessel

Mathematics, Rensselaer Polytechnic Institute
Kimberly's research focuses on developing a comprehensive nonlinear wave model for the governing physics of the transduction mechanism in the inner ear. This work requires a detailed analysis of the fluid-solid interaction dynamics of the cochlea, as well as the utilization of various perturbation methods and numerical techniques.

Wenrui Hao
Applied and Computational Mathematics and Statistics, University of Notre Dame
Wenrui applies numerical algebraic geometry methods and numerical partial differential equation methods to mathematical problems arising in biology, such as tumor growth, blood coagulation, and deriving efficient numerical methods for large scale computing. The mathematical tools that he uses include PDEs, numerical algebraic geometry, bifurcation analysis, and computational methods.

Paul Hurtado
Applied Mathematics, Cornell University
Paul's research integrates techniques from the fields of dynamical systems, stochastic processes and statistics to develop and analyze mathematical models motivated by questions in population ecology, infectious disease and immunology. He also pursues interesting mathematical questions that emerge from these applications.

Karly Jacobsen
Mathematics, University of Florida
Karly's research is focused on the spread and control of disease at a range of scales, from cells within a tumor to individuals and communities at the population level. She works in oncolytic virotherapy, the use of cancer-targeting viruses in the treatment of solid tumors, where she models spatial spread of viruses by cell-to-cell fusion as well as interactions of the tumor, virus, and immune response. Using analytical and numerical techniques, she analyzes the corresponding partial differential equation systems to investigate mathematical questions such as well-posedness and dynamical behavior as well as to gain clinical insights into tumor control. At the population level, Karly is interested in how the structure and seasonality of community and environmental networks affect the spread of infectious diseases such as cholera. Ordinary differential equations, dynamical systems, and graph theory are used to investigate disease dynamics.

Jae Kyoung Kim
Mathematics, University of Michigan, Ann Arbor
Jae's research has focused on developing theories and models to understand biological rhythms. Basic questions are: Is there an easier way to find hidden or unknown biochemical interactions? How do complex biochemical networks generate rhythms and control period? He has worked closely with several experimental groups in biology to develop new protocols to test model predictions.

Adrian Lam
Mathematics, University of Minnesota

Adrian is a Postdoctoral Fellow at the Mathematical Biosciences Institute (MBI) funded by Croucher Postdoctoral Fellowship. His research interest lies in the analysis of reaction-diffusion models arising from biology. His recent interest is to understand the effects of spatial heterogeneity and non-random transport in ecological models using an evolutionary gametheoretical approach.

Kang-Ling Liao
Applied Mathematics, National Chiao Tung University, Taiwan
Kang-Ling is interested in ordinary differential equations and dynamical systems. She focuses on the dynamics for gene expressions of somitogenesis in zebrafish. During the development of embryo, the clock gene expression exhibits synchronous oscillation in the tail bud and a traveling wave pattern arises from the posterior to the anterior of the presomitic mesoderm. The oscillation slows to a stop and cells form into somites. In order to investigate these phenomena, we considered the mathematical models which depict the kinetics of the zebrafish segmentation clock genes subject to direct autorepression by their own products under time delay, and cell-to-cell interaction through Delta-Notch signaling. The theoretical and numerical results not only provide some criteria and parameter regimes observed in somitogenesis, but also present how delays affect the dynamics of these models. Kang-Ling plans to perform similar methodologies to patch model in ecology to explore how delay affects the dynamics of the model and investigate the global dynamics of the model. She also plans to study the cancer immunoediting and attempt to construct a pertinent model which fits experimental data to investigate the mechanism of how tumor cells escape from the immune system.

Wing-Cheong (Jon) Lo
Mathematics, University of California, Irvine
Jon is particularly interested in analytic and computational analysis of biological models related to multi-stage stem cell lineages, tissue growth, morphogen-mediated patterning and budding yeast cell polarization patterns. He has been developing and analyzing a mathematical model to understand the formations of tissue stratification and stem cell niche with an application to olfactory epithelium. He is also studying the robustness of morphogen-mediated patterning in a noisy environment. While at MBI, he extends his research interest in modeling colorectal cancer and budding yeast cell. In addition, he is also interested in developing efficient and robust numerical tools for computing mathematical models of biological reaction-diffusion systems.

Leopold Matamba Messi
Applied Mathematics, University of Georgia
Leopold's interests are in mathematical image analysis, numerical analysis of partial differential equations, applied mathematics, and statistics. In his Ph. D. dissertation, he used finite difference and Galerkin methods to construct continuous piecewise polynomial approximations of the continuum TV-L2 image decomposition model. He plans to expand on this work to other total variation based image decomposition models. This includes the application of the stochastic Gillespie Algorithm to simulate ecosystems indicators within the Ecological Network Analysis framework. Currently, Leopold is collaborating with Julie Rushmore (Odum School of Ecology, University of Georgia) to study dynamics of the social network of the community of chimpanzees

of the Kibale National Forest (Uganda, East Africa), and its impact on disease transmission in the community.

Marcio Albasini Mourao
Indiana University
Márcio is interested in understanding how macroscopic behavior arises from simpler multiple interactions over time and space. He's currently investigating biological phenomena, but his long-term goal is to expand his research to biological, social, economical or even political systems. Márcio's work involves a combination of both theoretical and computational models.

Jay Newby
Mathematics, University of Utah
Jay's interests lie in stochastic processes and their application to biological problems. Although his primary area of focus is cellular neurobiology, he has also done work in intracellular transport, gene regulation, and population dynamics. During his time at MBI, Jay intends to investigate the link between the collective network behavior and cellular processes within an individual neuron, understand better how cellular processes (such as gene regulation) contribute to synaptic plasticity, and develop new perturbation methods to analyze rare events in jump Markov processes.

Michael A. Schwemmer
Applied Mathematics, University of California, Davis
Michael's research spans three spatial scales in the brain: from electrical activity of single cells and small networks, through the dynamics of neural populations, to models of behavior and cognition. At the cellular level, Michael studies how spatial properties modulate neuronal spiking dynamics; at the population level, and how neural substrates interact across multiple brain regions to integrate attention and decision making. At the behavioral level, he studies the limitations of human multitasking abilities. By building and analyzing models that connect aspects of these levels, he seeks to understand how biophysical and computational properties of neurons enable and constrain network activity and, ultimately, produce behavior.

Michal Seweryn
Biostatistics, University of Lodz
Michal's research is focused on the development of statistical models and methods for comparative analysis of sparse populations. Here, similarity is expressed both in terms of diversity, as well as overlap between communities. The main aim of the project is to provide tools for the statistical analysis of the immune system related, next generation sequencing data. The diversity analysis relies on information-theoretical concepts based on measures of entropy. In the study of overlap, notions associated with either measures of bivariate statistical dependence or geometrical relations between probability vectors are used. The crucial challenge is to establish methods which both: are robust to next generation sequencing errors and take into account low coverage of samples due to sparseness of populations. From this point of view the nonparametric approach is much more demanding than the more standard methods based on parametric models for count data. This approach was used to uncover relations between different (in terms of location and function) T-cell receptor populations in murine models.

Lucy Spardy
Mathematics, University of Pittsburgh
Lucy's research is in mathematical neuroscience, with a focus on the development and analysis of models that produce rhythmic motor patterns. She uses geometric singular perturbation theory, phase plane analysis, and other tools from dynamical systems theory to deduce the mechanisms responsible for oscillations in different networks. Her interest lies in understanding how features like network structure and sensory input collaborate to produce oscillatory behaviors. She is also interested in inferring the architecture of networks underlying distinct rhythms produced by shared muscles and motoneurons. Recordings from the central nervous system indicate that individual neurons participate in multiple behaviors, but for large systems like the vertebrate nervous system, this is insufficient to deduce the network structure responsible for rhythmicity. To approach this problem, Lucy constructed and simulated ODE models with different architectures for comparison with experimental results.

Marc Sturrock
Applied Mathematics, University of Dundee
Marc has studied a variety of areas including: spatio-temporal modeling, gene regulatory networks, negative feedback loops, intracellular signaling pathways, systems biology, and cancer modeling.

Ying (Joy) Zhou
Mathematics, University of Washington
Joy's research has focused on mathematical models for geographic range shifts of plants and animals under climate change. Math tools include deterministic and stochastic dynamical systems, integral operators, and PDEs.

C. MBI PUBLICATIONS IN 2013-2014

The following newsletter and publications were produced at the MBI during 2013-2014:

Newsletter
Autumn 2013, Volume 9, Issue 1

Publications

MBI PUBLICATIONS FOR 2013 (26)

1. Hu and D. Chen
   High-order fractional partial differential equation transform for molecular surface construction.
   *Molecular Based Mathematical Biology*Vol. 1 (2013)
2. H. Kang, M. Crawford, M. Fabbri, G. Nuovo, M. Garofalo, P. Nana-Sinkam and A. Friedman
   A mathematical model for microRNA in lung cancer
   PLoS ONE Vol. 8 No. 1 (2013)

3. S. Adams, C. Zhang, H. Zambrano and T. Conlisk
   Antibody-antigen binding in a flow-through microfluidic device
   51st AIAA Aerospace Sciences Conference (2013)
4. E. Martin, A. Friedman and W. Lo
   Mathematical Model of Colitis-associated Colon Cancer
   *Journal of Theoretical Biology*Vol. 317 (2013) pp. 2. 20-29
5. H. Park, C. Chou and W. Lo
   Polarization of Diploid Daughter Cells Directed by Spatial Cues and GTP Hydrolysis of Cdc42 in Budding Yeast.
   PLoS ONE Vol. 8 No. 2 (2013)
6. Diekman, C. Fall, J. Lechleiter and D. Terman
   Modeling the neuroprotective role of enhancing astrocyte mitochondrial metabolism during stroke
   Biophysical Journal (2013) (In Press)
7. Lam and Y. Lou
   Evolution of Conditional Dispersal: Evolutionarily Stable Strategies in Spatial Models
   Journal of Mathematical Biology (2013)
8. R. Azencott , A. Beri, A. Jain and I. Timofeyev
   Sub-sampling and Parametric Estimation for Multiscale Dynamics
   Communications in Mathematical Sciences (2013) (To Appear)
9. S. Liu, A. Matzavinos and S. Sethuraman
   Random walk distances in data clustering and applicationsAdvances in Data *Analysis and Classification*Vol. 7 No. 1 (2013) pp. 83-108
10. H. Kang and T. Kurtz
    Separation of time-scales and model reduction for stochastic reaction networks
    *Annals of Applied Probability*Vol. 23 No. 1 (2013) pp. 529-583
11. R. Azencott , A. Beri, Y. Gadhyan, N. Joseph, C. Lehalle and M. Rowley
    Realtime market microstructure analysis: online Transaction Cost Analysis
    Quantitative Finance (2013) (Submitted)
12. K. Liao, X. Bai and A. Friedman
    The role of CD200-CD200R in tumor immune evasion
    J. Theor. Biol. (2013) (Accepted)
13. Koslicki
    Quikr: a Method for Rapid Reconstruction of Bacterial Communities via Compressive Sensing
    Oxford Journal of Bioinformatics (2013) (Under Review)
14. V. Krivan and R. Cressman
    Competition in di-and tri-trophic food web modules
    *Journal of Theoretical Biology*Vol. 343 (2013) pp. 127-137
15. Diekman, C. Fall, J. Lechleiter and D. Terman
    Modeling the neuroprotective role of enhanced astrocyte mitochondrial metabolism during stroke.
    *Biophysical Journal*Vol. 104 No. 8 (2013) pp. 1752-63

16. M. Eisenberg, S. Robertson and J. Tien
    Identifiability and estimation of multiple transmission pathways in cholera and waterborne disease.
    *Journal of Theoretical Biology*Vol. 324 (2013) pp. 84-102
17. R. Cressman and V. Krivan
    Two-patch population models with adaptive dispersal: the effects of varying dispersal speeds
    *J. Math. Biol.*Vol. 67 (2013) pp. 329–358
18. K. Liao, X. Bai and A. Friedman
    The role of CD200-CD200R in tumor immune evasion.
    *Journal of Theoretical Biology*Vol. 328 (2013) pp. 65-76
19. Koslicki and S. Foucart
    Quikr: a method for rapid reconstruction of bacterial communities via compressive sensing.
    Bioinformatics (Oxford, England)Vol. 29 No. 17 (2013) pp. 2096-102
20. W. Lo, R. Arsenescu and A. Friedman
    Mathematical model of the roles of T cells in inflammatory bowel disease.
    *Bulletin of Mathematical Biology*Vol. 75 No. 9 (2013) pp. 1417-33
21. W. Hao and A. Sommese
    Completeness of solutions of Bethe's equations.
    *Physical review. E, Statistical, nonlinear, and soft matter physics*Vol. 88 No. 5 (2013) pp. 052113
22. M. Eisenberg, G. Kujbida, A. Tuite, D. Fisman and J. Tien
    Examining rainfall and cholera dynamics in Haiti using statistical and dynamic modeling approaches.
    *Epidemics*Vol. 5 No. 4 (2013) pp. 197-207
23. J. Chang, K. Brennan, D. He, H. Huang, P. Wilson and J. Wylie
    A mathematical model of the metabolic and perfusion effects on cortical spreading depression.
    PloS ONE Vol. 8 No. 8 (2013) pp. e70469
24. Diekman, M. Golubitsky and Y. Wang
    Derived patterns in binocular rivalry networks.
    *Journal of Mathematical Neuroscience*Vol. 3 No. 1 (2013) pp. 6
25. W. Lo, M. Lee, M. Narayan, C. Chou and H. Park
    Polarization of diploid daughter cells directed by spatial cues and GTP hydrolysis of Cdc42 budding yeast.
    PloS ONE Vol. 8 No. 2 (2013) pp. e56665
26. H. Kang, M. Crawford, M. Fabbri, G. Nuovo, M. Garofalo and A. Friedman
    A mathematical model for microRNA in lung cancer.
    PloS ONE Vol. 8 No. 1 (2013) pp. e53663

MBI PUBLICATIONS FOR 2014 (20)

1. F. Kloosterman, S. Layton, Z. Chen and M. Wilson
    Bayesian decoding of unsorted spikes in the rat hippocampus

Journal of Neurophysiology Vol. 111 No. 1 (2014) pp. 217-227
2. Lam and Y. Lou
   Evolutionarily stable and convergent stable strategies in reaction-diffusion models for conditional dispersal.
   Bulletin of Mathematical Biology Vol. 76 No. 2 (2014) pp. 261-91
3. K. Liao and Y. Lou
   The effect of time delay in a two-patch model with random dispersal.
   Bulletin of Mathematical Biology Vol. 76 No. 2 (2014) pp. 335-76
4. J. Newby and M. Schwemmer
   Effects of moderate noise on a limit cycle oscillator: counterrotation and bistability.
   Physical Review Letters Vol. 112 No. 11 (2014) pp. 114101
5. J. Chang and T. Chou
   Iterative graph cuts for image segmentation with a nonlinear statistical shape prior.
   Journal of Mathematical Imaging and Vision Vol. 49 No. 1 (2014) pp. 87-97
6. Lam and Y. Lou
   Evolution of conditional dispersal: evolutionarily stable strategies in spatial models.
   Journal of Mathematical Biology Vol. 68 No. 4 (2014) pp. 851-77
7. V. Krivan
   Behavioral refuges and predator-prey coexistence
   Journal of Theoretical Biology Vol. 339 (2014) pp. 112-121
8. P. Bressloff and J. Newby
   Path integrals and large deviations in stochastic hybrid systems.
   Physical review. E, Statistical, Nonlinear, and Soft Matter Physics Vol. 89 No. 4 (2014) pp. 042701
9. Matzavinos, B. Shtylla, Z. Voller, S. Liu and M. Chaplain
   Stochastic modeling of chromosomal segregation: Errors can introduce correction
   Bulletin of Mathematical Biology (2014)
10. J. Kim, Z. Kilpatrick, M. Bennett and K. Josic
    Molecular mechanisms that regulate the coupled period of the mammalian circadian clock
    Biophysical Journal Vol. 106 No. 9 (2014) pp. 2071–2081
11. L. Altenberg
    Evolvability and Robustness in Artificial Evolving Systems: Three Perturbations Genetic Programming and Evolvable *Machines* (2014) (In Press)
12. N. Beckman and H. Rogers
    Consequences of Seed Dispersal for Plant Recruitment in Tropical Forests: Interactions within the Seedscape
    Biotropica Vol. 45 No. 6 (2014) pp. 666-681
13. V. Billock and B. Tsou
    Bridging the divide between sensory integration and binding theory: Using a binding-like neural synchronization mechanism to model sensory enhancement during multisensory interactions.
    Journal of Cognitive Neuroscience Vol. 26 (2014) pp. 1587-1599 (In Press)
14. Ermentrout and V. Billock

Flicker-induced phosphenes
Encyclopedia of Computational Neuroscience Springer-Verlag (2014) (In Press)

15. L. Comita, S. Queenborough, S. Murphy, J. Eck, K. Xu, M. Krishnadas, N. Beckman and Y. Zhu
    Testing predictions of the Janzen–Connell hypothesis: a meta-analysis of experimental evidence for distance- and density-dependent seed and seedling survival
    Journal of Ecology Vol. 102 No. 4 (2014) pp. 845-856
16. J. Chang, V. Savage and T. Chou
    A path-integral approach to Bayesian inference for inverse problems using the semiclassical approximation
    Journal of Statistical Physics Vol. 157 No. 3 (2014) pp. 582–602
17. J. Chang and T. Chou
    Iterative graph cuts for image segmentation with a nonlinear statistical shape prior
    Journal of Mathematical Imaging and Vision Vol. 49 No. 1 (2014) pp. 87-97
18. K. Liao, X. Bai and A. Friedman
    Mathematical modeling of interleukin-27 induction of anti-tumor T cells response.
    PloS ONE Vol. 9 No. 3 (2014) pp. e91844
19. W. Hao and A. Friedman
    The LDL-HDL Profile Determines the Risk of Atherosclerosis: A Mathematical Model.
    PloS ONE Vol. 9 No. 3 (2014) pp. e90497
20. Diekman and M. Golubitsky
    Network symmetry and binocular rivalry experiments.
    Journal of Mathematical Neuroscience Vol. 4 (2014) pp. 12

D. 2013-2014 TOPIC SELECTION

To support the MBI 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 programs are aimed at bringing mathematical scientists and bioscientists together to discuss ways in which the mathematical sciences are being used to solve significant problems in the bio and biomedical sciences and how problems from the biosciences are opening new areas of research for mathematicians, statisticians, and computational scientists. The Director consults widely in the mathematical bioscience community for appropriate subjects for emphasis years. MBI encourages the wider mathematical and scientific communities to propose ideas for programs.

MBI activities involve input from the Board of Trustees, Scientific Advisory Committee, Local Scientific Advisory Committee, Emphasis Year External Advisory Committee and Workshop Organizers. Detailed information about each committee follows:

1. Board of Trustees (BOT)

Governance in program planning is provided by a Board of Trustees. The Board consists of individuals with leadership experience in the public and private sectors, and of recognized scientists in fields related to the MBI activities. The Board will meet annually to advise the directors and The Ohio State University regarding management of the institute, to review its scientific programs, and to suggest new programs and give advice regarding programmatic goals.

For 2013-2014, the Board included the following individuals and their terms:

1. Anna Barker, Arizona State University (January 2012 - December 2017)
2. Rita R. Colwell, University of Maryland, College Park (January 2009 - December 2013)
3. Rebecca Doerge, Purdue University (January 2014 – December 2016)
4. Irving Epstein, Brandeis University (January 2012 - December 2017)
5. Kirk E. Jordan (Chair), IBM T.J. Watson Research Center)January 2007 - December 2015)
6. Jim Keener, University of Utah (January 2012 - December 2017)
7. Nancy Kopell, Boston University (January 2013 - December 2015)
8. Claudia Neuhauser, University of Minnesota Rochester (May 2012 - December 2015)
9. Alan S. Perelson, Los Alamos National Laboratory (January 2012 – December 2017)
10. John Reinitz, The University of Chicago (January 2012 - December 2017)
11. Blake Thompson, Battelle Memorial Institute (January 2010 - December 2014)
12. Michael Waterman, University of Southern California (January 2010 – December 2015)

Past committee members:

1. John Guckenheimer, Cornell University (2009-2011)
2. Robb Krumlauf, Scientific Director, Stowers Institute for Medical Research, Kansas City, MO (2007-2010)
3. Barbara Kunz, President of Health and Life Sciences Global Business, Battelle, Columbus, OH (2007-2009)
4. Mark Lewis, University of Alberta (2007-2011)
5. Robert M. Miura, Department of Mathematical Sciences, New Jersey Institute of Technology, Newark, New Jersey (2007-2012)
6. Stephen Ruberg, Board of Directors, Member at National eHealth Collaborative, Senior Research Fellow at Eli Lilly (2007-2009)

2. Scientific Advisory Committee (SAC)

SAC reviews MBI programs and suggests and decides on annual programs and organizers. The Committee consists of internationally recognized mathematical scientists and bioscience researchers from academia and industry. SAC meets annually to review the institute programs, to suggest and decide on new annual programs, and to give advice regarding programmatic goals.

2013-2014 committee members and their terms:

1. Fred Adler, University of Utah (January 2014 – December 2016)
2. Alexander Anderson, H. Lee Moffitt Cancer Center (January 2011 - December 2013)
3. Paul Bressloff, University of Utah (January 2011 - December 2013)
4. Thomas Chou, University of California, Los Angeles (January 2012 – December 2015)
5. Dan Coombs, University of British Columbia (January 2014 – December 2016)
6. Chris Cosner, University of Miami (January 2011 - December 2013)
7. Domitilla Del Vecchio, Massachusetts Institute of Technology (January 2013 - December 2015)
8. Gerda deVries, University of Alberta (January 2011 - December 2013)
9. Tim Elston, University of North Carolina, Chapel Hill (January 2011 - December 2013)
10. Nina Fefferman, Rutgers University (January 2013 - December 2015)
11. Greg Forest, University of North Carolina, Chapel Hill (January 2011 - December 2013)
12. James Glazier, Indiana University (January 2013 - December 2015)
13. Abba Gumel, University of Manitoba (January 2013 - December 2015)
14. Alan Hastings, University of California, Davis (January 2014 – December 2016)
15. Trachette Jackson, University of Michigan (January 2012 - December 2014)
16. Nan Laird, Harvard University (January 2012 - December 2014)
17. Reinhard Laubenbacher, University of Connecticut Health Center (January 2011 - December 2013)
18. Sharon Lubkin, North Carolina State University (January 2011 - December 2013)
19. Michael Mackey (Chair 2014), McGill University (January 2011 - December 2015)
20. Qing Nie, University of California (January 2010 - December 2015)
21. Mette Olufsen, North Carolina State University (January 2014 – December 2016)
22. Javier Rojo, University of Nevada (January 2014 – December 2016)
23. Jonathan Rubin, University of Pittsburgh (January 2013 - December 2015)
24. Santiago Schnell, Brehm Center for Diabetes Research, University of Michigan (January 2014 – December 2016)
25. Hal Smith, Department of Mathematics and Statistics, Arizona State University (January 2014 – December 2016)
26. Jack Tuszynski, University of Alberta (January 2012 - December 2014)

Past committee members:

1. Reka Albert, Physics, Pennsylvania State University
2. Linda Allen, Mathematics, Texas Tech University
3. Adam Arkin Howard Hughes, Medical Institute, Bioengineering, University of California, Berkeley
4. Herb Bresler, Health and Life Sciences, Battelle Memorial Institute, Columbus, OH
5. Mark Chaplain, The SIMBIOS Centre, Mathematics, University of Dundee
6. Thomas Daniel, University of Washington
7. Mark Denny, Biology, Stanford University
8. Leah Edelstein-Keshet, Mathematics, University of British Columbia
9. Bard Ermentrout, Mathematics, University of Pittsburgh
10. Lisa Fauci, Mathematics, Tulane University

11. Louis Gross, The Institute for Environmental Modeling, Ecology & Evolutionary Biology, Mathematics, The University of Tennessee
12. Shandelle M. Henson, Andrews University
13. Sorin Istrail, Center for Computational Molecular Biology, Computer Science, Brown University
14. Nicholas P. Jewell, Biostatistics and Statistics, University of California, Berkeley
15. Kirk Jordan, IBM Computational Biology Center, Yorktown Heights, NY
16. Jim Keener, Mathematics, University of Utah
17. Douglas Lauffenburger, Biological Engineering, Chemical Engineering, Biology, Massachusetts Institute of Technology
18. Suzanne Lenhart, Mathematics, University of Tennessee
19. Naomi Leonard, Princeton University
20. Mark Lewis, Mathematical and Statistical Sciences, University of Alberta
21. Andre Longtin, University of Ottawa, Canada
22. Gregory Mack, Environmental Monitoring and Assessment, Battelle Memorial Institute, Columbus OH
23. Paul Magwene, Biology, Duke University
24. L. Mahadevan, Harvard University
25. Philip Maini, Centre for Mathematical Biology, Mathematical Institute, University of Oxford
26. Claudia Neuhauser, Ecology, Evolution, and Behavior, University of Minnesota
27. Karl J. Niklas, Plant Biology, Cornell University
28. Lior Pachter, Mathematics, University of California, Berkeley
29. Alan Perelson, Theoretical Biology and Biophysics Group, Los Alamos National Laboratory
30. Linda Petzold, Mechanical and Environmental Engineering, Computer Science, University of California, Santa Barbara
31. Mike Reed, Mathematics, Duke University
32. John Rinzel, Center for Neural Science and the Courant Institute of Mathematical Sciences, New York University
33. Stephen Ruberg, Clinical Data Technology and Services, Eli Lilly and Company, Indianapolis
34. Steven Rust, Battelle Memorial Institute
35. Stanislav Shvartsman, Chemical Engineering, Princeton University
36. James Sneyd, Mathematics, University of Auckland, New Zealand
37. Terrence Speed, Statistics, University of California, Berkeley
38. John Taulbee, Epidemiology and Biometrics Division, Procter & Gamble Company, Cincinnati
39. Terry Therneau, Biostatistics, Mayo Clinic College of Medicine, Rochester, MN
40. Frank Tobin, Scientific Computing & Mathematical Modeling, GlaxoSmithKline
41. John Tyson, Biology, Virginia Polytechnic Institute and State University
42. Steven Vogel, Biology, Duke University
43. Michael S. Waterman, Mathematics, University of Southern California

44. Raimond L. Winslow, Center for Cardiovascular Bioinformatics & Modeling, Whitaker Biomedical Engineering Institute, and Biomedical Engineering, The Johns Hopkins University School of Medicine and Whiting School of Engineering

3. Local Scientific Advisory Committee (LSAC)

The LSAC consists of members of The Ohio State University community. It helps identify current topics workshops, suggest ideas for future emphasis programs and organizers, and potential mentors for postdoctoral fellows.

2013-2014 committee members and their terms:

1. Irina Artsimovitch, Microbiology (July 2011 - June 2014)
2. Ralf Bundschuh, Physics (July 2010 - June, 2013)
3. James Cogdell, Mathematics (July 2010 - June 2013)
4. Meg Daly, Evolution, Ecology, and Organismal Biology (July, 2009 - June 2015)
5. Andrea Doseff, Heart and Lung Research Institute, Molecular Genetics,and Internal Medicine (July 2011 - June 2014)
6. Martin Feinberg, Chemical Engineering (July 2010 - June 2013)
7. Avner Friedman, Mathematics (July 2009 - June 2015)
8. Tim Huang, Center for Integrative Cancer Biology (- 2014)
9. Kay Huebner, Molecular Virology, Immunology and Medical Genetics (July 2011 - June 2014)
10. Doug Kniss, Obstetrics and Gynecology (July 2011 - June 2016)
11. Gustavo Leone, Molecular Virology, Immunology, and Medical Genetics (July 2009 - June 2015)
12. Shili Lin, Statistics (July 2010 - June 2016)
13. Thomas J. Magliery, Chemistry (July 2010 - June 2016)
14. Stuart Mangel, Neuroscience (July 2010 - June 2016)
15. Elizabeth Marschall, Evolution, Ecology, and Organismal Biology (July 2010 - June 2016)
16. Deborah Parris, Molecular Virology (July 2010 - July 2013)
17. Roger Ratcliff, Psychology (July 2010 - June 2016)
18. Wolfgang Sadee, Pharmacology (July 2009 - June 2015)
19. Larry S. Schlesinger, Infectious Diseases, Microbial Interface Biology (July 2009 - June 2015)
20. Chandan Sen, Surgery (July 2009 – June 2015)
21. Amanda Simcox, Molecular Genetics (July 2009 - June 2015)
22. Parthasarathy Srinivasan, CSE, Biomedical Informatics (July 2014 – June 2016)
23. Don Stredney, Research Department (July 2009 - June 2015)
24. Joe Travers, Neuroscience (July 2011 - June 2014)

Ex Officios:

1. Janet Best, Mathematics
2. Helen Chamberlin, Molecular Genetics
3. Marty Golubitsky, MBI

4. Laura Kubatko, Department of Statistics
5. Tony Nance, MBI
6. Dennis Pearl, Department of Statistics
7. Greg Rempala, MBI
8. Andrej Rotter, Pharmacology

Former Committee Members:

1. Erich Grotewold, Deptartment of Plant Cellular and Molecular Biology, The Ohio State University
2. Richard Hart, Biomedical Engineering, The Ohio State University
3. Dan Janies, Deptartment of Biomedical Informatics, The Ohio State University
4. Stanley Lemeshow, Biostatistics, The Ohio State University
5. Yuan Lou, Department of Mathematics, The Ohio State University
6. David Terman, Mathemathics Department, The Ohio State University

4. Workshop Organizers

The 2013-2014 year was the first in which MBI hosted separate Emphasis Semester programs.

The Autumn Semester 2013 program was on Ecosystem Dynamics and Management. The Organizing Committee was: Jordi Bascompte (Integrative Ecology Group, Estacio n Biolo gica de Donana, Consejo Superior de Investigaciones Cientıficas, Sevilla, Spain;), Chris Cosner (Department of Mathematics, University of Miami), Alan Hastings (Department of Environmental Science and Policy, University of California, Davis), Marc Mangel (Center for Stock Assessment Research, University of California, Santa Cruz), Jim Sanchirico (Department of Environmental Science and Policy, University of California, Davis), and Mary Lou Zeeman (Department of Mathematics, Bowdoin College).

The Spring Semester 2014 program was on Frontiers in Imaging, Mathematics, and the Life Sciences. The Organizing Committee was: Monica Hurdal (Department of Mathematics, Florida State University), Paul Kulesa (Developmental Biology, Stowers Institute for Medical Research), Mauro Maggioni (Mathematics, Duke University), Allen Tannenbaum (Computer Science and Applied Mathematics, Stony Brook University), and Ross Whitaker (School of Computing, University of Utah).

E. MBI WORKSHOP REPORTS

Reports for Events in 2013-2014:

Current Topic Workshop: Teaching Discrete and Algebraic Mathematical Biology to Undergraduates
July 29- August 2
Organizers: Raina Robeva (Sweet Briar College), Matt Macauley (Clemson University), Terrell Hodge (Western Michigan University)
Report by: Franziska Hinkelmann, Paul Hurtado, Rachel Leander

Amended by: Raina Robeva, Matt Macauley, Terrell Hodge

The main goal for the workshop was to bring together mathematicians and biologists interested in developing new undergraduate curricular materials that demonstrate the power of discrete and algebraic methods for solving problems in modern biology. The two major goals for the workshop were to: 1) Introduce current problems from biology that utilize discrete and algebraic methods at a level appropriate for undergraduates and outline the methods, models, and software as well as existing materials with examples, exercises, and projects; 2) Produce outlines of new curricular materials based on some of the workshop talks on topics for which no materials for undergraduate courses are available.

The workshop activities were comprised of lecture-style talks, followed by "hands-on" sessions and small-group activities focused on developing the module outlines. During the latter sessions, participants worked on problems connected to the talk, suggested additional exercises, discussed ways in which the materials could be used with students in different types of courses, gained exposure to specialized software, and initiated drafts for the educational modules.
Brief summaries of the talks are presented below.

MONDAY, JULY 29, 2013

Developing one day to one week drop-in modules for undergraduate classrooms In Mathematical Biology
Margaret Cozzens (Rutgers University)
Dr. Cozzens began with a brief history of module development at the Center for Discrete Mathematics and Theoretical Computer Science (DIMACS). Initially, modules were developed as part of teacher workshops and were intended to encourage interdisciplinary cooperation in teaching at the high school level. DIMACS modules in mathematical biology are now the basis of high school courses that are currently being offered in the states of North Dakota, Massachusetts, Montana, and Missouri.

Dr. Cozzens went on to explain the process of module development: In creating a new module DIMACS begins by selecting a new module topic, author, and target grade-level. The module's author is responsible for selecting content and preparing materials. After many years of module development, Dr. Cozzens has found that the most important part of module development is the identification of goals. That is, one must identify the skills or knowledge that a module hopes to teach. In addition, every module should include a student assessment in order to be certain that a module meets its goals. After outlining the process of module development Dr. Cozzens illustrated the process with a brief description of three modules: Imperfect Testing, Tomography, and NJ Weather.

In producing modules, DIMACS also implements its own field tests. The most common complaints that DIMACS receives from pilot module teachers are that the module does not contain enough information to guide the teacher, and that there is not enough time to incorporate the

module into the course. It is important to keep these difficulties in mind when designing a new module.

Algebraic models in systems biology
Reinhard Laubenbacher (University of Connecticut Health Center)
Professor Laubenbacher's talk focused on several types of discrete models. Progress in systems biology relies on the use of mathematical and statistical models for systems-level studies of biological processes. Several different modeling frameworks have been used successfully. He illustrated construction and use of discrete models via two case studies, one related to breast cancer, the other to respiratory fungal infections, both in the context of the role of iron metabolism.

Graphs, food webs, and biodiversity.
Margaret Cozzens (Rutgers University)
Dr. Cozzens began her introduction to modeling food webs with discrete models (graphs) with the foundational work of Fred Roberts during the 1960s and 70s. This talk presented materials that could be used in undergraduate biology and mathematics classes related to using graph models of complex trophic relationships, determining the importance of a particular species or relationship in a food web, and using competition graphs to determine the dimension of the habitat that structures the focal community. After discussing predator-prey relationships, trophic levels, dominant species, ecosystem stability, and related biological concepts, Dr. Cozzens introduced competition graphs, interval graphs, Benzer's problem and boxicity, the competition number, and ways to use this modeling framework to study food webs. Dr. Cozzens concluded with discussion of related open problems in mathematics.

If life is analog, why are we being so discrete?
John Jungck (University of Delaware)
Dr. Jungck began with a brief overview of the important mathematical contributions that have shaped the biological sciences, and the recent widespread interest in mathematical applications in biology, including applications of graph theory, which the speaker would argue is "the natural language of biology." The majority of the talk addressed a number of examples in each of the following graph theoretic concepts: (1) One-dimensional Interval Graphs; (2) Two-dimensional (Planar) Graphs, e.g., Voronoi Tessellations; (3) Three-dimensional Graphs or Polytopes; (4) x.y-dimensional Graphs, Fractals; (5) Trees; (6) Networks; (7) Paths and Circuits; and (8) Bipartite Graphs. The speaker also discussed software like BENZER, BioGrapher, and Ka-Me, that provide empirical scientists with access to these tools. Biological applications included DNA and other molecular-level sequence data, RNA folding, cell shapes, classification of viruses, phylogenetic trees, and many more.

Combinatorics of RNA secondary structure
Svetlana Poznanović (Clemson University)
Dr. Poznanović began with an overview of the many roles RNA plays in shaping cell structure and function, and the importance of understanding how an RNA sequence folds into 3D structures. The limitations of current methods for predicting these 3D structures from the RNA sequence alone were then discussed, highlighting the importance of predicting the 2D secondary structure

as an important intermediary step., Starting from RNA as a simple sequence of nucleotides (bases), the secondary structure of an RNA molecule represents the sequence folding arising from naturally occurring base pairings and other biological constraints; secondary structures can be represented by planar figures with well-known motifs (e.g., hairpin loops) and described in several equivalent ways mathematically. Dr. Poznanović then surveyed some of the graph-theoretic and formal language approaches used to analyze secondary structures, with emphasis on those accessible to undergraduate students. These included asymptotic enumeration of possible secondary structures for a length-*n* molecule using combinatorial and graph theoretic concepts like context-free grammars, and tools like the software Pfold and relating different structures using trees.

Topology and combinatorics of RNA structures
Christian M. Reidys (University of Southern Denmark)
Dr. Reidys introduced the treatment of RNA secondary structures as pseudoknots, and biological evolution as a process that moves through the space of pseudoknot structures. He also presented results assuring the recovery of RNA secondary structure diagrams along a given path through a space of pseudoknots. Thus, the path encodes instructions for building one (pseudoknot) structure from another. Dr. Reidys then described how RNA pseudoknot structures can be represented not just by graphs, but by a fat graph, which is a graph embedded on a higher-genus surface. This extra information is encoded by a cyclic ordering of the edges at each vertex. It is of interest to employ the fatgraphs because, while pseudoknot structures cannot be generated recursively on their crossing number, they can be generated recursively on the genus of the corresponding fat graph. This can be done by passing to the Poincaré dual, which switches vertices and boundary components, yielding a new fat graph. Importantly, this allows a classification structure and a method of constructing and deconstructing these objects via gluing and slicing. There are only 4 irreducible shapes that generate all such structures. Dr. Reidys ended with discussion of how, using this framework, there may exist a linear time algorithm for sampling RNA structures and interaction structures. Empirically, the majority of RNA structures are comprised of only 2 of the 4 structures, rarely are 3 required, and almost never are all 4 required. The theory developed so far for RNA secondary structures will likely also provide a general detangling method to obtain normal forms (and sampling schemes) for more complex networks. Dr. Reidys is currently working on developing this approach for arbitrary graphs. While a full treatment of the topics would require some working notions from fundamental topology expanding more deeply into moduli spaces and beyond, and thus be appropriate for upper-level undergraduates or graduates, there are many related combinatorial results of interest, along with initial explorations of the RNA secondary structures as pseudoknots and then fat graphs, that, through the hands-on presentation of Dr. Reidys, could be made accessible to lower-level undergraduates.

TUESDAY, JULY 30, 2013

BioModel engineering - a Petri Net perspective
Monika Heiner (Brandenburg University of Technology, Cottbus, Germany)
Dr. Heiner described a Petri net-based framework to model and analyze biochemical networks, such as gene regulatory, signal transduction or metabolic networks. The framework comprises the qualitative, stochastic, and continuous modeling paradigms. Each perspective adds its contribution

to the understanding of the system. Dr. Heiner also discussed hybrid Petri nets, which combine the stochastic and continuous modeling paradigms to model processes across multiple temporal scales, and the use of colored Petri nets to model multiple spatial scales. Colored Petri nets combine a broad range of Petri nets with finite or discrete data types, permitting concise representations of regularly structured nets. For example they can statically encode hierarchically structured discrete space. Throughout her talk, Dr.Heiner introduced the computational, multi-functional and freely available toolkit that exists to support this framework: (1) Snoopy - a tool for modeling and simulation of hierarchical qualitative, stochastic, continuous, and hybrid Petri nets, and their colored counterparts; (2) Charlie - analysis tool of standard Petri net properties; and (3) Marcie - which performs symbolic reachability analyses of qualitative Petri nets, and both analytical and simulative model checking of stochastic Petri nets.

Fitness landscapes: geometric and discrete approaches
Kristina Crona (University of California, Merced)
Dr. Crona discussed mathematical models of fitness and adaptation. She began by introducing the concept of a *fitness landscape*, which is a surface of genotypes in which height corresponds to a genotype's fitness. An uphill walk over a landscape corresponds to the process of adaptation. After introducing fitness landscapes, Dr. Crona explained how models of evolution over fitness landscapes can be used to predict and prevent the emergence of antibiotic resistant bacteria. She went on to describe how fitness landscapes are formed. In particular, she explained how interactions between genes can lead to complex fitness landscapes with multiple peaks and valleys. The interaction of genes for fitness is called epistasis. Several paradoxes, including the paradox of sex, can be explained by epistasis. Dr. Crona spent the remainder of her talk describing new mathematical approaches to understanding epistasis and adaptation, focusing, in particular, on fitness landscapes and epistasis. She described several different types of epistasis, including *sign epistasis* in which single deleterious mutations are advantageous when they occur simultaneously. It has been shown that sign epistasis is necessary for a fitness landscape to have multiple peaks and valleys. Dr. Crona concluded her talk with a brief description of the geometric theory of gene interactions or shape theory, where the *shape* of a fitness landscape is an induced triangulation of the genotype.

WEDNESDAY, JULY 31, 2013

Dynamics of Disease Transmission Networks
Winfried Just (Ohio University)
Dr. Just described methods and principles of modeling disease transmission. He began by describing directly transmitted diseases, and then discussed the sort of questions that epidemiologists hope disease models can answer. For example: Will there be an epidemic? What proportion of the population will be infected? What control methods will be effective? When deciding between models, Dr. Just discussed the virtue of choosing the simplest model that can effectively answer your questions. He went on to outline some simplifying assumptions that can be used to create deterministic compartmental models of disease transmission, termed SEIR models. These models use differential equations to describe the number of susceptible, exposed, infected, and recovered hosts. Dr. Just showed that these models are tractable and can be used to

answer many important questions. In particular, they can predict if a single infection will spark an epidemic. However, they ignore stochasticity and the structure of the contact, so their predictions may not be accurate enough. In particular, epidemiologists quantify a disease's potential to start an epidemic in terms of its *basic reproductive number*. This number represents the average number of secondary infections that will arise if a single infected individual is introduced into a population of susceptible individuals. The deterministic SEIR model allows one to determine the basic reproductive number of a disease in terms of the transmission and recovery rates and predicts that an epidemic will occur if and only if the basic reproductive number is greater than one. In practice however, the number of secondary infections arising from a single infected individual may depend on the infected individual's contact network and be subject to stochasticity. Dr. Just then explained how one can simulate a stochastic model of disease transmission over a contact network. He showed that such a model is useful in predicting the probability of an epidemic and in identifying network features that are important determinants of an epidemic's final size and probability.

Discrete dynamic modeling of signaling networks
Réka Albert (Penn State University)
Professor Albert first reviewed the basics of Boolean modeling, with special attention to models that allow different timescales in the system (i.e. asynchronous models). She presented an asynchronous Boolean model of the signaling network that governs plants' response to drought conditions. This model synthesizes a large number of independent observations into a coherent system, reproduces known normal and perturbed responses, and predicts the effects of perturbations in network components. Two of these predictions were validated experimentally. In the second part, she presented an asynchronous Boolean model of the signaling network that is responsible for the activation-induced cell death of T cells (a type of white blood cell). Perturbations of this network were identified as the root cause of the disease T-LGL leukemia, wherein T cells aberrantly survive and then attack normal cells. The model integrates interactions and information on certain components' abnormal states, explains all the observed abnormal states, and predicts manipulations that can abolish the T-LGL survival state. Several of these predictions were validated experimentally. She concluded by presenting two methods for extracting useful predictions from Boolean models of signal transduction networks without extensive simulations.

Reduction of discrete models
Alan Veliz-Cuba (University of Houston)
Dr. Veliz-Cuba introduced reduction methods for Boolean and multi-state models. Boolean networks have been successfully used in modeling gene regulatory networks. However, for large networks, analysis by simulation becomes unfeasible. In his talk, Dr. Veliz-Cuba described and illustrated reduction methods for Boolean networks that decrease the size of the network while preserving important dynamical properties and topological features. The reduced networks could then be used to better understand the properties of the original network.

Methods to reverse engineer biological networks
Brandilyn Stigler, Mathematics, Southern Methodist University

Professor Stigler's talk explained reverse engineering methods for discrete biological networks. Gene regulatory networks are ubiquitous in molecular systems biology and contribute to the control of major biological processes including metabolism and development. Given the abundance of gene data sets, the ability to reconstruct the regulatory network underlying the data has become one of the prime objectives in systems biology research. She introduced various methods for *reverse-engineering* or inferring the structure of gene regulatory networks. These methods use techniques from computational algebra and algebraic geometry to build models of polynomial dynamical systems, which provide a rich backdrop within which to perform network analyses. Dr. Stigler showed some algebraic models and simulated how one could use them to design biologically meaningful models in an experimental setting.

THURSDAY, AUGUST 1, 2013

Algebraic methods for molecular phylogenetics
Ruriko Yoshida (University of Kentucky)
Dr. Yoshida began by describing her experience designing and realizing interdisciplinary courses for students interested in learning about mathematical and computational approaches to the life sciences. In particular, she told the audience about a graduate course in phylogenetic analysis and molecular evolution in which students from the life sciences, statistics, and computer science completed interdisciplinary group projects. Dr. Yoshida went on to introduce species trees and phylogenetic trees. A species tree depicts how various species evolved from a common ancestor. A phylogenetic tree depicts how a gene evolved in a group of related species. Dr. Yoshida then briefly introduced various mathematical approaches that are used to infer the structure of phylogenetic trees, including maximum likelihood estimation methods, the balanced minimum evolution method, and Bayesian methods. In the remainder of her talk Dr. Yoshida talked in more detail about the balanced minimum evolution method. In particular, she introduced several tree moves that are commonly used for tree reconstruction and also defined a distance matrix which records the distance between any two leaves of a tree. Dr. Yoshida concluded her talk with some results about trees and distance matrices.

All speakers were advised by the organizers to prepare their talks at a level appropriate for an undergraduate audience. Dr. Laubenbacher's talk was an exception as its goal was to present examples of recent advances in systems biology based on the use of algebraic models (thus the connection to undergraduate education was indirect). By and large, the speakers succeeded remarkably well in connecting topics from their current research with concepts and methods that are generally already present in the undergraduate mathematics curriculum. The talks provided a whole host of important and interesting biological questions to which the theory could be applied. The follow-up small group activities provided an opportunity for the participants to gain a better understanding of the theory and to brainstorm about possible ways for incorporating the material into the undergraduate curriculum. In the few cases when the talks were at a somewhat higher level (e.g. Christian Reidys' or Monika Heiner's talks), the small group discussions focused on possible ways for "breaking down" the big ideas into smaller segments that are individually less challenging but would collectively imply the general theory.

At the end of the workshop, the participants formed "working groups" charged with continuing work on specific modules in collaboration with the workshop presenters. The groups are expected to prepare sets of notes, comments, suggested exercises, and solution keys for the module outlines, while the workshop organizers will assemble the final outline. The activities of these groups are still ongoing. The topics for the modules under preparation are listed below. The exact titles of the modules have not been determined yet.

- Food webs and graphs
- Fitness landscapes
- Disease transmission on a network
- Combinatorics of RNA secondary structures
- Topology of RNA structures and folding
- Discrete dynamics modeling of signaling networks
- Reduction of Boolean networks
- Phylogenetic tree reconstruction
- Modeling with Petri nets

The module outlines are currently in various stages of development. The goal is to have them ready and to forward them for posting on the MBI's site by the end of November, 2013.

Building upon the workshop's goals, Raina Robeva has now received a contract from Academic Press for an edited volume of undergraduate modules on algebraic and discrete methods for modern biology. The volume will feature substantially expanded versions of the outlines developed at the workshop into individual book chapters co-authored by the workshop presenters and participants, as appropriate. Other authors, including the workshop organizers Matt Macauley and Terrell Hodge, will contribute additional chapters. Each chapter will begin with a question from modern biology, followed by the description of the mathematical methods and theory appropriate in the search of answers. Many of the projects and exercises will utilize specialized software, exemplifying the notion that familiarity and experience with computing applications which implement the mathematical theory are critical elements of the "modern biology" skill set. The target date for delivering the final drafts of the chapter-modules is June 1, 2014. The expected publication date for the volume is in the spring of 2015.

Workshop for Young Researchers in Mathematical Biology
August 26-29, 2013
Organizers: The MBI Postdoctoral Fellows.
Report by: Wing Cheong Lo and Michael Schwemmer

MONDAY, AUGUST 26, 2013

A Statistical Approach for Detecting Copy Number Variations for Next Generation Sequencing Data
Claudia Neuhauser (University of Minnesota)
In this talk, Dr. Neuhauser spoke about DNA detecting copy number variations (CNV), which are genetic signatures for complex diseases such as cancer. CNVs are caused by deletion or

duplication of genes within chromosomes. Cancer researchers hope to discover specific CNVs that are significant in different types of cancer. High-throughput sequencing technologies combined with efficient mapping algorithms enable fast detection of CNVs.

Dr. Neuhauser proposed a statistical approach to finding CNVs that might be significant in cancers. To ascertain statistical significance of candidates, she proposed a mathematical model for the distribution of mapped read counts together with a statistical. The model assumes that reads are mapped to a reference genome. By partitioning the genome, she was able to determine the nth read count, defined as the number of nucleotides starting in the n-the partition. She assumed that the read counts form an m-dependent, strictly stationary stochastic process and that they are Poisson distributed with a parameter that varies across the genome. This variation is modeled with a gamma distribution. The model was validated using genome data from four genomes that are presumed to lack CNVs. The test was based on extremes of the number of mapped reads in consecutive windows, and thus avoids the problem of multiple hypothesis testing.

Modeling and Analysis of the Population Dynamics of Fungus-Infected American Chestnut Populations

Eric Alan Eager (University of Wisconsin-La Crosse)

Dr. Eager's talk regarded matrix population models of the American Chestnut and chestnut blight. Density-dependent regulatory factors impact the dynamics of many populations. However, modelers often consider only one density-dependent factor when constructing nonlinear structured population models, and these factors are often either always increasing or always decreasing with respect to population abundance. In his presentation, Dr. Eager discussed his density-dependent matrix model for populations of the American Chestnut (Castanea dentata). In contrast to previous density-dependent models, seedling recruitment is assumed to be subject to two kinds of density-dependent feedback. The first is from the population of adult conspecifics, which decreases seedling recruitment. The second type is from other potential seedlings, which has a have a positive effect on seedling recruitment. For example, adult chestnut trees may create too much shade for a nearby seedling to survive. On the other hand, producing a larger number of seeds and seedlings results in more surviving to adulthood.

He found that, for much of the parameter space, there is a unique, globally attracting equilibrium population vector that is independent of initial population vector. He presented a formula for this equilibrium population and showed how sensitive each stage of the population is to changes in population data. For example, the situation changes significantly when chestnut blight enters the population and causes some plants to become diseased. He also discussed extending his results to integral projection models (IPMs) and numerically explored some stochastic versions of this model.

Optimal Fishery Harvesting on a Nonlinear Parabolic PDE in a Heterogeneous Spatial Domain

Michael Kelly (University of Tennessee)

In his talk, Dr. Kelly considered the problem of maintaining fish populations in the face of overexploitation of fisheries. The importance of this problem has been apparent as fish populations shrink. The overexploitation of fisheries has called for an improved understanding of

spatiotemporal dynamics of resource stocks as well as their harvesters. Dr. Kelly focused on predicting the effect of no-take marine reserves, which prohibit the removal of natural resources from an area of the ocean, on these dynamics. All previous work done has assumed that when fish leave the no-take reserves they die, i.e. that reserves have Dirichlet boundary conditions. Instead, he considered whether the implementation of alternative boundary conditions on a heterogeneous domain could produce an alternative optimal harvesting strategy. By using Robin boundary conditions, he found that these optimal solutions include no-take marine reserves. He can then find the harvest rate that maximizes the discounted yield. These optimal strategies were found numerically.

Population Persistence in the Face of Uncertainty
Sebastian Schreiber (University of California, Davis)
In his talk, Dr. Schreiber presented two of his perspectives on the following question: "What conditions ensure the long-term persistence of interacting populations?" Historically, this question has been tackled using deterministic difference and differential equations. By considering first demographic and then environmental stochasticity, his models considered persistence in the face of uncertainty.

The first part of his talk considered demographic stochasticity when a population consists of a finite number of individuals. Stochastic models predict extinction of all populations in finite time. Despite the inevitability of extinction, Dr. Schreiber found that under some conditions extinction events may be preceded by long-term transients characterized by the quasi-stationary distributions of the stochastic process. His work with Mathieu Faure showed that these quasi-stationary distributions concentrate on attractors of an appropriate deterministic difference equation, thus providing justification for using deterministic models to study long-term persistence.

The second part of his talk considered the effects of environmental stochasticity, assuming that fluctuations in environmental conditions cause fluctuations in vital rates of populations. He defined persistence for stochastic models to be a statistical tendency for populations to remain bounded away from extinction. He presented his work with Gregory Roth, where it was shown that there is a sufficient condition for stochastic persistence in terms of the population growth rates when rate. He then looked at the possibility of competition between species in the face of environmental stochasticity, and concluded that there are conditions under which coexistence can occur.

Optimal Control of Female-Killing Strategies to Eliminate the Dengue Vector, Aedes Aegypti
Michael A. Robert (North Carolina State University)
Dr. Robert's research considers the problem of controlling the spread of Dengue fever, which is endemic in many parts of the world. Since the Dengue vector *Aedes aegypti* prefers to live in urban areas and preferentially feeds on humans, dengue fever is spread primarily by this type of mosquito. Recently, control strategies involving the release of genetically modified mosquitoes have been proposed. While some of these strategies focus on interfering with the ability of *Ae. aegypti* to produce viable offspring, the strategies that have seen the most progress are Female-Killing (FK) strategies. One such strategy creates male mosquitos with a female killing (FK) gene to mate with wild type females. The female progeny of the GM mosquitos will die, while ½ of

male progeny will carry the FK gene. Cage experiments showed that repeated introductions of individuals from this FK strain of *Ae. aegypti* led to either reduction or extinction of caged wild-type populations. Dr. Robert pointed out that future open releases should be conducted according to plans that consider temporal and financial constraints. To this end, he has developed an optimal control model to assess the role that such constraints will play in conducting FK releases. Through numerical simulation, he presented optimal release strategies for a variety of scenarios and to consider the feasibility of integrating FK releases with other forms of vector control.

Adaptive Evolution of Dispersal: A Population Approach
King-Yeung Lam (Mathematical Biosciences Institute)
Dr. Lam discussed evolutionary stable strategies (ESS) for competing phenotypes in a spatially varying but temporally constant environment. A strategy is an ESS if once a population has adapted it, it cannot be invaded by a mutant with another strategy. He considered what an ESS might be in a heterogeneous, patchy environment. To answer this question, he first considered a result by Hastings: in the absence of biased movement or advection, the mutant can invade when rare if and only if it has smaller random dispersal rate than the resident. He assumes that each phenotype performs a small amount of biased movement or advection, resulting in a reaction-diffusion equation. He concludes based on his analysis of the model that the existence of an ESS depends upon the spatial heterogeneity of the environment and that if that ESS does exist, its rate of diffusion and rate of directed movement will be proportional.

TUESDAY, AUGUST 27, 2013

Bistability of Beta Cell Mass in Diabetes
Arthur Sherman (NIH)
Dr. Sherman's talk focused on current research into Type II Diabetes, especially the function of beta cells. Beta cells consume glucose and produce insulin, the master hormone that controls fuel usage by body tissues. It was once assumed that insulin resistance drove the development of diabetes, and that the beta cells were affected only after a patient became diabetic. Research in diabetic rats now suggests that beta cells become more massive in pre-diabetes, as insulin resistance also develops. This process may occur in order to compensate for higher insulin requirements. By updating Topp et al (J. Theor. Biol. 2001)'s model for the regulation of beta-cell mass by glucose, Dr. Sherman presented a comprehensive picture of how diabetes develops and may either be avoided or reversed. He then showed that this model results in a bistable bifurcation structure, with normal and elevated glucose levels separated by a threshold. He went on to use this bistability to explain experimental results, including why prevention is much easier than cure and why bariatric surgery is able to reverse longstanding diabetes within a week.

Mathematical Modeling of Pharmaceuticals: Predictive Design for Better Medicines
Ashlee N. Ford-Versypt (MIT)
Dr. Ford-Versypt's talk applied mathematical techniques to the pharmaceutical industry. Formulation manufacturing results in delivery mechanisms for drugs. One newer delivery mechanism is edible polymer film containing a drug. This film is produced using a drying process, where the temperature and time period for optimal moisture content were unknown. Dr. Ford-

Versypt worked discussed her mathematical model, concluding that decreasing the temperature during the drying process results in the fastest production of polymer. A newer research project involves controlled release forms of medications. These formulations are able to sustain a therapeutic concentration for a longer period of time, resulting in longer periods of time between doses. Models coupled with process control strategies allow for careful monitoring of manufacturing to reduce wasted materials and energy and to adhere to quality standards. Her work work related to predicting drug release from controlled-release formulations. Using a reduced system of coupled, nonlinear partial differential equations, she was able to successfully model the biodegradation of the pharmaceutical formulation that strongly influences the drug release dynamics. These techniques can aid in the design of new controlled release formulations.

Optimal Allocation of Insecticides for Leishmaniasis Control: A Case for Bihar, India
Anuj Mubayi (Northeastern Illinois University)
Dr. Mubayi's presentation suggested a solution to Leismaniasis infection in regions where it is endemic. Leishmaniasis is a parasite that kills approximately 50,000 people per year, primarily in poor and developing countries. Most of these deaths occur when a patient contracts the visceral type of this disease, in which multiplying parasites destroy organs. The Indian state of Bihar has the highest prevalence and mortality rates of visceral Leishmaniasis (VL) in the world. Insecticide spraying is a primary vector control method in many parts of the world for controlling spread of VL. Dr. Mubayi's model optimized the insecticide-induced death rate caused by spraying of human and bovine populations dwellings within the constraint of limited financial resources available in Bihar. He concluded that the optimal solution depends on the goal of the spray campaign. When the goal is to prevent infections short term or when a second spraying is scheduled soon, a minimum number of houses and a maximum number of cattle sheds should be treated. On the other hand, for long term prevention without a second treatment, a maximum number of houses should be treated. Dr. Mubayi continues to research the effect of multiple treatments over time.

How Good are Mathematical Models of Genetic Signaling Networks?
Kresimir Josic (University of Houston)
Dr. Josic presented his thoughts on models of genetic circuits, with the eventual goal of being able to determine the behavior of an engineered genetic circuit within given parameters. He briefly reviewed an ordinary differential equation model for a simple negative feedback circuit. In this circuit, a gene produces a protein, which in turn signals the cell to downregulate the production of that protein. The ODE model is less accurate than one that takes into account "transcriptional delay" - the delay between the start of protein production and the time a mature protein finds a downstream target. Such delay can inhibit transitions between states of bistable genetic networks, as well as destabilize steady states in other networks. Dr. Josic suggested using reduced, non-Markovian models instead, and presented two possible paths to analyzing these models. His first approach came from queuing theory. This approach suggests that, if the associated deterministic system was bistable, the bistability of the non-Markovian system is determined by the mean length of the transcriptional delay. His second approach involved a Langevin Approximation of the system. Dr. Josic remained unsure whether the analysis of this approximation corresponded with the original system. He went on to describe an application to circadian oscillators. These projects

remain ongoing.

WEDNESDAY, AUGUST 28, 2013

Biofluids of Reproduction
Lisa Fauci (Tulane University)
Dr. Fauci first introduced some basic facts about reproduction and explained the role of fluid dynamics in successful implantation of embryo. The process of fertilization in mammalian reproduction provides a rich example of fluid-structure interactions. Spermatozoa encounter complex, non-Newtonian fluid environments as they make their way through the cilia-lined, contracting conduits of the female reproductive tract. The beat form realized by the flagellum varies tremendously along this journey due to mechanics and biochemical signaling. The speaker presented recent progress and several simulations on integrative computational models of pumping and swimming in both Newtonian and complex fluids that capture elements of this complex dynamical system.

A Mathematical Model of Intimal Thickening: an Application to Atherosclerosis
Pak-Wing Fok (University of Delaware)
In this talk, Dr. Fok discussed how to use mathematical model to understand atherosclerosis, an inflammatory disease of the artery characterized by an expansion of the intimal region. Intimal thickening is usually attributed to the migration of smooth muscle cells (SMCs) from the surrounding media and proliferation of SMCs already present in the intima. Intimal expansion can give rise to dangerous events such as stenosis (leading to stroke) or plaque rupture (leading to myocardial infarction).

The speaker proposed a mathematical model of intimal thickening, posed as a free boundary problem. Intimal thickening is driven by damage to the endothelium, resulting in the release of cytokines and migration of SMCs. By coupling a boundary value problem for cytokine concentration to an evolution law for the intimal area, the problem was reduced to a single nonlinear differential equation for the luminal radius. The speaker analyzed the steady states, performed a bifurcation analysis, and compared model solutions to data from rabbits whose iliac arteries are subject to a balloon pullback injury. In order to obtain a favorable fit, he concluded that migrating SMCs must enter the intima very slowly compared to cells in dermal wounds. This cell behavior is indicative of a weak inflammatory response, which is consistent with atherosclerosis being a chronic inflammatory disease.

Dynamics of Additional Food Provided Predator-prey System with Mutually Interfering Predators
Sree Rama Vara Prasad Bhuvanagiri (Vellore Institute of Technology)
This talk is about the role of mutual interference on the success of biological control programs when predators are provided with additional food in predator-prey system. Use of additional/alternative food source to predators is one of the widely recognized practices in biological control. Both theoretical and experimental works point out that quality and quantity of additional food play a vital role in the controllability of the pest. Theoretical studies carried out

previously in this direction indicate that incorporating mutual interference between predators can stabilize the system.

In this study, the speaker studied the dynamics of additional food provided predator-prey system with mutual interference between predators. The mutual interference between predators is modeled using Beddington-DeAngelis type functional response. The results indicate the possibility of stable coexistence of predators with low prey population levels. This is in contrast to classical predator-prey models where in this stable co-existence at low prey population levels are not possible. This study classifies the characteristics of biological control agents and additional food of suitable quality and quantity, permitting the eco-managers to enhance the success rate of biological control programs.

Reverse Engineering Crosstalk in Neutrophil Polarity Network
Lani Wu (UT Southwestern Medical Center)
In this talk, Dr. Wu discussed recent progress in using perturbation analysis and cellular heterogeneity to constrain network crosstalk from cellular behaviors. A central question in biology is how complex, spatial-temporal cellular behaviors arise from biochemical networks. Much work has led to the identification and cataloguing of various network architectures, and the explication of how static network motifs can give rise to dynamic response characteristics, including ultrasensitive, switch-like, and oscillatory behaviors. However, the wiring diagrams of signaling networks are often inferred by combining results from diverse assays. Such diagrams may not represent accurately the operating state of the network in any cell, condition or time point. Dr. Wu applied perturbation analysis and cellular heterogeneity to study neutrophil polarity which relies on local, mutual inhibition to segregate incompatible signaling circuits to the leading and trailing edges. Mutual inhibition alone should lead to cells having strong fronts and weak backs or *vice versa*. However, analysis of cell-to-cell variation in human neutrophils revealed that back polarity remains consistent despite changes in front strength. Pharmacological perturbations and mathematical modeling revealed a new functional role for microtubules to buffer back polarity by mediating positive, long-range crosstalk from front to back; loss of microtubules inhibits buffering and results in anti-correlation between front and back signaling.

Asynchronousity in Boolean Networks
Matthew Macauley (Clemson University)
Dr. Macauley first introduced Boolean networks through a motivating example, the *lac* operon in *E. coli*. A Boolean network consists of a finite set of nodes, each taking a Boolean state, and each having an update function depending on a subset of the other states. These functions are assembled to get the dynamical system map which is iterated to generate the dynamics. The common synchronous function update is convenient but often biologically unnatural. In contrast, asynchronousity poses questions about stability and robustness with respect to update order. In this talk, Dr. Macauley introduced toric posets which can be thought of as a cyclic version of ordinary posets and provided a clean combinatorial framework for describing asynchronousity in Boolean networks.

A stoichiometric Producer-Grazer Model Incorporating the Effects of Excess Food-Nutrient

Content on Consumer Dynamics
Angela Peace (Arizona State University)
The speaker started with a brief talk about the Lotka-Volterra Producer-Grazer model and ecological stoichiometry. While the effects of nutrient deficiency on consumer growth are well understood, recent discoveries in ecological stoichiometry suggest that consumer dynamics are not only affected by insufficient food nutrient content, low phosphorus (P): carbon (C) ratio, but also by excess food nutrient content, high P:C. This phenomenon is known as the stoichiometric knife edge, in which animal growth is reduced not only by food with low P content but also by food with high P content, and needs to be incorporated into mathematical models. In this talk, Lotka-Volterra type model was applied to investigate the growth response of Daphnia to algae of varying P:C ratios capturing the mechanism of the stoichiometric knife edge.

Thursday, AUGUST 29, 2013

Irreversible Transitions, Bistability and Checkpoints in the Eukaryotic Cell Cycle
John Tyson (Virginia Tech)
In this talk, Dr. Tyson discussed that cell cycle transitions are irreversible because of systems level feedback leading to bistability. Progression through the eukaryotic cell cycle is controlled at a series of checkpoints guarding transitions from one phase of the cycle to the next. These checkpoints ensure that a cell has satisfied certain requirements that are necessary for success of the next phase. These transitions are irreversible: as soon as the conditions of the checkpoint are satisfied, the cell proceeds to the next phase and does not subsequently back up to the immediately preceding phase.

Molecular geneticists have discovered the genes and proteins governing these checkpoints, but the mechanistic basis of irreversibility is still a subject of controversy. Many molecular biologists think that the transitions are irreversible because key proteins are chemically degraded at each transition, but the speaker showed that irreversibility is a consequence of bistability and hysteresis in the underlying regulatory network. To prove this claim, Dr. Tyson described the mechanisms of the G1-S and metaphase-anaphase transitions, built and analyzed a mathematical model of the mechanisms, and compared the implications of the model to experimental facts.

The Effect of MicroRNA-Mediated Feedforward Loops on Gene Regulatory Networks
Claus Kadelka (Virginia Tech)
In this study, the modeling framework of generalized Boolean networks was applied to explore the role that microRNA-mediated feedforward loops play in stabilizing the global dynamics of various gene regulatory networks. The concept of canalization in gene regulation was developed as a possible solution to the question of why the outcome of embryonic development leads to predictable phenotypes in the face of widely varying environmental conditions. The key step of gene expression is fundamentally a stochastic process, which makes the stability of genetic regulation programs all the more surprising. An entirely novel gene regulatory mechanism, discovered and studied during the last decade and which is believed to play an important role in cancer, is shedding some light on how canalization may in fact take place as part of a cell's gene regulatory program. Short segments of single-stranded RNA, so-called microRNAs, which are

embedded in several different types of feedforward loops, help smooth out noise and generate canalizing effects in gene regulation by overriding the effect of certain genes on others.

Through computational study, the speaker compared the degree of stochasticity of a basic gene network and an extended network, in which various numbers of microRNAs have been introduced in a biologically inspired way, and were thereby able to exactly quantify the stabilizing effect for any gene regulatory network.

Mathematical modeling of pronuclear rotation in the nematode C. elegans embryo
Valerie Coffman (The Ohio State University)
In the first part of the talk, the speaker explained what pronuclear rotation in the nematode *C. elegans*. In preparation for division, cells must position the nucleus in order to properly segregate chromosomes and other factors. During the first cell cycle of the nematode worm *C. elegans*, the male and female pronuclei meet at the posterior pole of the embryo, and the entire pronuclear complex migrates to the center of the cell. Simultaneously a 90-degree rotation of the centrosomal axis occurs. Centrosomes serve as microtubule organizing centers for the mitotic spindle during cell division. The microtubule minus-end directed motor protein dynein is essential for correct nuclear positioning and spindle orientation. Due to the symmetric distribution of dynein, at the cortex and in the cytoplasm of the early embryo, it is not clear how the forces required to rotate the pronuclear complex are generated.

The speaker hypothesized that the pronucleus rotates during translocation due to unequal cortical forces acting on the two centrosomes independent of stochastic microtubule dynamics. She proposed a project with three main objectives. The first objective will be to take in vivo measurements of forces on the centrosomes during nuclear centering and rotation using a confocal microscope. The measurements will be taken in embryos dissected out of the adult worm after fertilization and in situ. From these measurements, physical parameters such as torque, angular velocity, acceleration and momentum will be calculated. The second objective will be to use these measurements and calculations to develop mechanical models of the nuclear rotation event. Third, predictions of the model will be tested in vivo using genetic knockdowns and other molecular techniques.

Autumn Emphasis Semester Workshop 1: Sustainability and Complex Systems

September 16-20, 2013
Organizers: Chris Cosner (University of Miami), Volker Grimm (Karlsruhe Institute of Technology), Alan Hastings (University of California), and Otso Ovaskainen (University of Helsinki)
Report by: Noelle Beckman, Joy Zhou, and Márcio Mourão

MONDAY, SEPTEMBER 16, 2013

Aquaculture and Sustainability of Coastal Ecosystems
Mark Lewis (University of Alberta)

In this talk, Dr. Lewis showed an example of the impact of aquaculture to the natural ecosystem, which is the facilitation of parasitic sea lice infestation on wild salmon by salmon farms in British Columbia. With high salmon density in salmon farms, the farms may be disease reservoirs that act as stepping-stones to transmit sea lice from adult wild salmon to juvenile wild salmon. In contrast, in a natural ecosystem without these farms, the chance of such transmission is low. The main question asked was: are salmon farms causing more sea lice infections in juvenile wild salmon? To answer this question, researchers sampled and analyzed spatial data of sea lice that have successfully attached themselves to wild juvenile salmon. They obtained detailed data of sea lice in its different life stages, and found a spatial footprint of a salmon farm from the data. The data suggested that sea lice on juvenile wild salmons increase near a farm along the salmon migration route, and the sea lice go through their life stages while being carried by migrating salmon. This may harm the wild salmon population. Researchers showed this with models and data for salmon survival, which demonstrated that higher lice density leads to higher mortality in juvenile wild salmon. They also developed hierarchical models of stock-recruitment dynamics and found that salmon farms were reducing the number of returning salmon. The good news is, sea lice treatment is available, and can be effective, though expensive. Historical data show that treating lice on farm salmon before the spring migration of juvenile salmon is better for the wild salmon than treating later in the season. Finally, a recent and ongoing project is looking at behavior changes of juvenile salmon after sea lice infestation. These behavior changes make juvenile salmon potentially easier to prey upon, causing parasite-mediated predation.

Modeling socio-economic aspects of ecosystem management and biodiversity conservation
Yoh Iwasa (Kyushu University)
In this talk, Dr. Iwasa presented models that consider social and economic influences on the management target. Three models were presented. The first model analyzes coupled socio-economical and ecological dynamics for phosphorous pollution in lake water. Players choose between cooperative (but costly) option and economical option, and their decision is affected both by the fraction of cooperators in the community and by the seriousness of water pollution problem. Oscillation of large amplitude appeared if social change occurs faster than ecosystem responses. Also, the model shows a "paradox of nutrient removal". If phosphorus is removed more effectively either from the inflow or from the lake water, the pollution level may increase (rather than decrease) due to people's reduced social concern and therefore unwillingness to cooperate. The second model discusses how activities that promote social concern about biodiversity help to maintain public support for biodiversity conservation. The speaker talked about optimal investment in the trade-off between activities that increase social concern and those that maintain and improve the conservation target. The third model analyzes punishment as a mechanism to maintain cooperative behavior in a social group. It was shown that graduated punishment is the most efficient way to ensure cooperation when evaluation errors are unavoidable and when the social group is heterogeneous with respect to the sensitivity of its members to utility difference.

TUESDAY, SEPTEMBER 17, 2013

Individual-based Ecology
Volker Grimm (Karlsruhe Institute of Technology)

Dr. Grimm discussed the utility of individual-based models (IBMs) when individual variability, local interactions, and adaptive behavior need to be incorporated in modeling efforts. He outlined the standard protocol that was developed for describing IBM's. The ODD protocol consists of three blocks: Overview, Design Concepts, and Details. Dr. Grimm raised two problems associated with individual-based models: 1) models tend to be ad-hoc and 2) whether we can use these models to test hypotheses when it is difficult or impossible to validate because of lack of data. Dr. Grimm then proposed a framework of pattern-oriented modeling to analyze individual-based models, in which multiple patterns observed at different scales are used to analyze models. He gave an example of management of a pest, the coffee borer, using black-throated warblers, which compete for insects and use different habitats to forage. With this model, four alternative hypotheses of foraging theory were tested using patterns emerging from the dynamics of bird populations. Dr. Grimm suggested the fundamental problem for IBMs is developing theory for individual behavior that explains system dynamics and recommended models focus on specific dynamics of specific systems. For future directions, he suggested the development of theories beyond individual behavior and strategies to separate signal from noise. Dr. Grimm discussed different approaches that can be used to deconstruct an IBM that would result in an analytical mathematical model or statistical model consisting of essential components.

Sustainability of agroecosystems: insights from the multiscale insect pest monitoring
Sergei Petrovskii (University of Leicester)
Dr. Petrovskii discussed how to infer mechanisms resulting in spatial synchrony from data sampled at different scales. Spatial synchrony can arise from dispersal among habitats or environmental stochasticity, known as the Moran effect. A big challenge is distinguishing these two mechanisms. In his case study, he discussed the population dynamics of the European crane fly *Tipula paludosa*, a common pest in Europe and North America. Based on the cross-correlation coefficient, there was significant synchronization of population dynamics across fields over fourteen years. Synchronization across fields with no time delay was most likely due to the Moran effect, but the time-lagged synchronization found after one year was most likely due to dispersal coupling. Next he discussed how to estimate population sizes from sparse data. He found that numerical integration with varying weights taking into account space was a better estimate than the spatially implicit arithmetic mean. Better accuracy of numerical integration occurs when the inter-trap distances are on the order of the peak width. To determine whether population counts taken locally reflect regional population density, an individual-based approach can be used to simulate insect movement.

A network-patch modeling framework for the transmission of vector-borne infections
Mac Hyman (Tulane University)
Dr. Hyman discussed a hybrid modeling approach that integrates individual level-behavior at one-level and continuum differential models at another level. After discussing the benefits and costs of each type of modeling, he discussed two examples in which he applied a hybrid approach. The first example was of the chytrid fungus that infects amphibians. He used an individual-based model for individual frogs, and a SIR model with diffusion (partial differential equations) to model the spread of the fungus. In the second example, Dr. Hyman discussed a network-patch model developed with colleagues for the spread of mosquito-borne pathogens, including chikungunya,

dengue, and West Nile virus. The model accounted for the movement of individual people through mosquito habitats that responded to environmental factors, such as rainfall and temperature. Their approach extended the capabilities of existing agent-based models for human movement developed to predict the spread of directly transmitted pathogens in human populations. These agent-based models were combined with differential equations representing clouds of mosquitoes in geographic patches that account for heterogeneity in mosquito density, mosquito emergence rates, and the extrinsic incubation period of the pathogen. The new hybrid agent-based/differential equation model can help quantify the importance of heterogeneity in predicting the spread and invasion of mosquito-borne pathogens and extend the capabilities of existing agent-based models to include vector-borne diseases.

A trait-based perspective of complex systems
Priyanga Amarasekare (University of California)
Dr. Amarasekare discussed populations and communities in the context of complex systems, whose properties result from the interplay between non-linear feedbacks that are intrinsic to the system (e.g., biotic interactions that lead to density- and frequency-dependence) and external inputs (e.g., abiotic factors) that are outside the feedback structure of the system. To understand this interplay, she explored how the effects of external inputs on lower levels of the system (e.g., traits of organisms) influence properties at higher levels (e.g., population viability, species diversity). Using temperature as the axis of abiotic variation, Dr. Amarasekare developed a mechanistic theoretical framework for elucidating how abiotic effects on traits translate into population dynamics and species coexistence, and how these ecological dynamics in turn feedback into the trait response, causing trait evolution. Dr. Amarasekare tested model predictions with data on insects, using the Harlequin bug with two parasitoids as a model system.

WEDNESDAY, SEPTEMBER 18, 2013

Stochasticity in complex systems
Karen Abbott (Case Western Reserve University)
In this talk, Dr. Abbott discussed the effects of stochasticity in ecological dynamics. She presented two, not necessarily mutually exclusive, hypotheses for stochasticity outcomes. Stochasticity can make the dynamics fuzzier and/or produce a qualitative change in behavior. The speaker specifically discussed the effects of stochasticity in models with alternative stable states using models of predator-prey dynamics and insect outbreaks. She used three potential key signatures of alternative states in stochastic ecological dynamics: the mean density should be near equilibrium; populations will be more variable for alternative states; and the distribution of population sizes will look less unimodal. The data showed that these signatures were not very effective when applied to the predator-prey model. However, when noise is applied to the insect outbreak model, it appears to decrease the range of parameters that provide bistability as well as to steep the potential well at the equilibrium point. Other questions raised by the speaker were: which type of unstable states masquerade as noisy stable states? How does the dynamical behavior change for different stochastic perturbations? What are the most informative measures of stability for ecological applications? Although these questions remain largely unanswered, it is clear that stochasticity can have big effects in the dynamical behavior.

Rate-induced Tipping: Critical Rates, Non-obvious Thresholds and Failure to Adapt to Changing External Conditions

Sebastian Wieczorek (University of Exeter)

Complex systems may transit from one stable state to another. This is often referred to as "tipping". A well-studied type of tipping occurs when the external condition, described by parameters in the model, is at a critical level. This type of tipping can be studied with bifurcation diagrams. Here, Dr. Wieczorek presented a different tipping mechanism termed the "rate-induced tipping". In this tipping mechanism, tipping occurs when parameters change beyond a critical rate, as opposed to a critical level, while the stable state exists continuously for all fixed levels of external conditions and never bifurcates. These non-autonomous instabilities cannot be captured by classical bifurcation theory and remain fairly unexplored. Dr. Wieczorek presented an approach based on geometrical singular perturbation theory to study critical rates of change and non-obvious tipping thresholds. Dr. Wieczorek also discussed repercussions for climate change policy making which currently focuses on critical levels of the atmospheric temperature whereas the critical factor may be the rate of warming rather than the temperature itself.

Challenges in Modeling Biological Invasions and Population Distributions in a Changing Climate

Chris Cosner (University of Miami)

In this talk, Dr. Cosner discussed the challenges in modeling population dispersal and invasion from the perspective of a changing underlying environment. While typical models focus on at most a pair of species with fixed attributes and interactions, these assumptions often become invalid in the context of climate or environmental change. In this context, the structure of the model is regarded as a function of time, which brings numerous mathematical challenges. Presenting us with some classical models in population ecology literature, Dr. Cosner talk focused on three major issues. First, climate change may affect how species interact over time and space. Some of the current models analyze this problem by distributing members of two or more species in a finite number of patches, and making transitions between patches occur with some frequency over time. However, different species may have time dependent and different diffusion coefficients that lead to significant systemic behavioral differences. This poses numerous challenges and leads to the ultimate question: to what extent do species interactions affect geographic distributions and vice-versa? Second, climate change may affect the time at which species or resources emerge, affecting the system's dynamical behavior. How can we then develop models to study this type of phenomena denominated 'phenology matching'? Possible solutions would have to explicitly incorporate parameters that would describe the timing of events such as emergence. Third, because climate change may impose novel selection pressures of species invading a new region, Dr. Cosner proposes to incorporate evolutionary processes in modeling environmental changes. The talk finished with a discussion of the mathematical challenges to model the increasing complexity. One emerging consensus is that a synergy of both mathematical and computational models is desirable.

THURSDAY, SEPTEMBER 19, 2013

Role of time scales in sustainability of complex systems

Alan Hastings (University of California)
Dr. Hasting's talk was divided into three main parts: dynamics of coral recovery in an algal coral grazer system; multistability and warning signs in ecological dynamical systems; and active versus passive restoration of ecological systems. In the first part, the speaker described an extension of an analytical model to macroalgae and coral dynamics to analyze the effects of over-harvesting of herbivorous reef fish in the Caribbean. Herbivores play a critical role regulating the competitive relationship between microalgae and corals. When herbivores are not present, the faster growing microalgae can overgrow corals, depriving them of essential sunlight that causes their decline. Dr. Hasting's model allows the development of recommendations for different scenarios of coral reef recovery. The model identifies critical fishing effort levels and demonstrates that the coral recovery time scale depends on the fishing effort level. The second part of the speaker's talk was about averting catastrophic regime shifts in complex natural systems through early detection. The speaker showed that error rates can be strong for common indicators and presented a model-based approach to quantify the trade-off between reliability and sensitivity as well as to allow comparisons between different indicators. The speaker concluded that the performance of a warning indicator depends on the dataset and that uncertainty quantification may be the key to reliable warnings. In the last part of the talk, Dr. Hastings linked economics to ecological system's restoration strategies to conclude that there is an economical as well as a biological restoration threshold. He also concluded that restoration is profitable only below the economical restoration threshold and that a rule of thumb of any restoration is: restore until growth rate equals benefit to marginal cost ratio.

Coarse-graining computations for complex systems
Yannis Kevrekidis (Princeton University)
In this talk, Dr. Kevrekidis presented a framework that allows one to perform macroscopic computational tasks using microscopic simulations on short time and length scales. The framework bypasses the derivation of explicit macroscopic equations when these equations conceptually exist but are not available in closed form. The framework is then designed for a class of problems, which one observes evolution at a macroscopic, coarse scale, but accurate models are only given at a more detailed level. Dr. Kevrekidis approach is focused on a particular class of complex problems, distinct from two other types of systems he introduced, namely simple and complicated problems. The speaker started by introducing microscopic and macroscopic behavior with a multi-agents problem of buying and selling products in a one-dimensional scale. When some complexity is introduced at the microscopic level (i.e., agents interacting with each other), the macroscopic behavior can be very sensitive to the details of this microscopic behavior. For example, when interactions are in place, one can obtain clear departures from the macroscopic mean behavior where all agents end up either selling or buying the product. The speaker then formally introduced his approach with an example of a multivariable system whose derivative exists but is unknown. A key tool is the coarse time-stepper, i.e., a short computational experiment with the fine-scale simulator that consists of three main steps: lifting; simulation and restriction. The speaker then guided us through three main applications of his approach. The first is to compute steady states, which can be done by perturbing 'intelligently the initial conditions and run short burst of simulations. The second application is to the design of controllers, specifically designed to transform unstable into stable states. The third application demonstrated that the approach could

also be applied to models that include a spatial component. Finally, the speaker linked applications of his approach with recent developments in data mining algorithms, exploring large complex data sets to find low dimensional descriptors.

Tipping Points in Contagion Models
Carl Simon (University of Michigan)
In this talk, Dr. Simon presented a procedure for computing the basic reproduction number R_0, a tipping point, using Lyapunov functions. R_0 is a function of model parameters that allow us to determine whether or not zero is a stable equilibrium. Although it can be used in a variety of applications, the R_0 is a very well known metric in disease spreading. If $R_0<1$, the disease will die out in the long run. However, if $R_0>1$, the disease will be able to spread in the population. For simple models, the proportion of the population that needs to be vaccinated to prevent sustained spread of the infection is $1-1/R_0$. For low dimensional systems, one can compute R_0 using the eigenvalues of a matrix. However, that task becomes cumbersome for high dimensional systems. In those situations, Dr. Simon proposes to find R_0 using Lyapunov functions and presents several applications of it. The first is a compartmental model of HIV disease spread. The second is a dynamical model of crime spread using three variables, which he later expanded to five variables. Dr. Simon used this example to explain how the use of the derivative of R_0 with respect to key parameters, such as law enforcement use, can be very useful to understand potential intervention measures. The speaker also presented a model of staff disease infection in a hospital, starting with nine variables and making a few assumptions to reduce it to two variables. This model leads to two basic reproductive numbers whose product needs to be lower than one for the eradication of the disease in the long run. The talk ended with considerations about key assumptions made in all these models. Importantly, R_0 assumes random mixing and different people may have different contact probabilities with other people. In the presence of power law distributions for those interactions, one may need to look at disease spread in different structural networks and for the effect, write computer simulations of network-based models.

FRIDAY, SEPTEMBER 20, 2013

Beyond the proof of concept: virtual ecologists in complex dynamic systems
Damaris Zurell (University of Potsdam)
Dr. Zurell formed her talk around the idea of virtual ecologists. The virtual ecologist is an intuitive and widely used approach which includes simulating artificial species or ecosystem data, an observer that collects data according to a specific sampling protocol, the statistical analysis or modeling of the collected data and subsequent evaluation of the results against known (virtual) truth. To illustrate the idea, Dr. Zurell demonstrated many examples from ecological studies on many topics. For example, in global change research, the virtual ecologist approach holds great potential for rigorous testing of different modeling methods under controlled and changing conditions and with controlled sampling bias. Specifically, the speaker emphasized the merit of using complex dynamic simulation models for simulating data and observers. This ingredient takes the virtual ecologist approach beyond simple proof of concept making it a truly integrative and rigorous framework not only for testing sampling protocols or modeling and analysis tools, but also for theory development and testing more generally.

Models and data: from individuals to populations
Otso Ovaskainen (University of Helsinki)
Dr. Ovaskainen discussed how to derive analytical approximations from individual based-models using spatial cumulants. He gave an example of analyzing a spatial-temporal point process using a spatial logistic model that included reproduction, dispersal, and density-dependent mortality. This work builds on previous work using spatial moments, but is a better approximation. They use perturbation theory to show that the cumulant equations are asymptotically exact. This approach has many applications, including prediction of the time to the first encounter between searcher and targets, ecological and evolutionary dynamics in heterogeneous space, and evolution of dispersal.

Autumn Emphasis Semester Workshop 2: Rapid Evolution and Sustainability

October 7-11, 2013
Organizers: Jim Cushing (University of Arizona), Katia Koelle (Duke University), Patrick De Leenheer (Oregon State University), Stephan Munch (University of California, Santa Cruz)
Report by: Wenrui Hao, Paul Hurtado, Joy Zhou

MONDAY, OCTOBER 7, 2013

Eco-evolutionary dynamics: linking models to live systems
Gregor Fussmann, Biology, McGill University
In this talk, Dr. Fussmann presented three examples of eco-evolutionary dynamics. The first example is plankton predator-prey dynamics in a laboratory setting (i.e. chemostats). It was observed empirically that the predator and the prey populations oscillate completely out of phase, which is not explained by classic predator-prey theory. The speaker and his collaborators therefore tried to explain the phenomenon through the perspective of multi-genotype prey consistence. The second example is about resistance of parasites in a host-parasitoid guppy-monogenean system. This example is in a field study instead of a laboratory setting, and there was a surprising find that relaxed selection (absence of parasites) leads to increased resistance in this complex field situation. The third example is about evolutionary rescue for species experiencing extensive environmental change. The model presented is for evolutionary rescue at the community level, and it employs the Armstrong-McGehee formulation for two predators competing for the same prey. It was shown that, not only can evolutionary rescue occur in a single-species model, it can also occur in multi-species setting.

The evolutionary biology of drug resistance
Troy Day, Mathematics and Statistics, Queen's University
This talk was focused on the topic of drug resistance and treatment strategies. Dr. Day presented three sets of models. The first model was based on queuing theory. The idea was that there are two types of interventions we could take to increase the number of effective drugs in the drug supply pool. One is to slow down evolution of drug resistance, and the other is to speed up the development of new drugs. The model shows that the former is more effective than the latter because the former also increases the drug lifespan. The second model looks at the problem of

optimal treatment plan to minimize the outbreak size of an infectious disease. This population-level model found that the current practice of maintaining high treatment rate for a long period of time is not necessarily the best. If treatment rate is constant over time, an intermediate rate of treatment is better; and if treatment rate can vary over time, it is actually the timing of treatment that matters. In other words, the strategy of waiting until the susceptible pool size reaches a level, and then turn on the treatment rate to the maximum possible achieves smallest outbreak size. Of course, this delay-in-treatment strategy is not always to the best benefits of individuals. Dr. Day then presented a third model for the individual level perspective. At the individual level, it is found that using a cofactor to maintain host immune response state, such as depleting the pathogen of a crucial resource it needs, is effective in both wiping out the wild type strains and preventing the drug-resistant strains from breaking out.

Rapid evolution and the sustainable management of hatcheries and aquaculture
Marissa Baskett, Environmental Science and Policy, University of California
In this talk, the speaker talked about management strategies of salmon hatcheries and aquaculture farms in terms of releases or escapes of salmon from these facilities. These releases and escapes may cause harmful fitness changes in the wild salmon population once the released salmon mate with the wild population. The speaker presented coupled demographic-quantitative genetic models applied to wild fish populations that receive inputs from hatcheries or aquaculture. For hatcheries, model analysis indicates that a "segregated hatchery" approach of breeding a different population to reduce interactions with the wild population can provide a viable alternative to an "integrated hatchery" approach of breeding a similar population to reduce fitness effects only if a strong natural selection event occurs between hatchery release and reproduction. This relative efficacy, conditional on the ordering of life cycle events, holds for the aquaculture case of comparing the relative fitness consequences of an extremely maladapted (i.e., nonlocal-origin, highly domesticated) stock to a weakly diverged cultured stock. Aquaculture model results also indicate that imperfect sterilization can still substantially reduce unintended fitness consequences, and that reducing escapees through low-level leakage is more effective at minimizing unintended fitness consequences than reducing an analogous number of escapees from large, rare pulses. These models apply insights from the theory of gene flow and local adaptation to the management of artificial propagation and extend that theory to include new dynamics such as assortative mating and variable exchange in time.

Rapid evolution of hosts and ecological host-parasite dynamics
Meghan Duffy, Ecology & Evolutionary Biology, University of Michigan
In this talk, the speaker presented a host-parasitoid system where the ecological dynamics and the evolutionary dynamics interact with each other closely. The host is a zooplankter *Daphnia dentifera*, and a fungal parasite *Metschnikowia bicuspidate*. Infected host individuals suffer from reduced reproduction, increased mortality rates and are observed to not recover. It was found that the host evolves rapidly and develops resistance against infection, and that the type of evolution that occurs is influenced by the ecological context in which the host-parasite interaction is embedded. It was shown that rapid evolution of host resistance can fundamentally alter ecological dynamics, driving the termination of parasite epidemics. It was also found that there are tradeoffs between resistance and fecundity. While tradeoffs can strongly impact rapid evolution, they are

rarely studied in natural populations. It was found that there is variation in costs of resistance in wild host populations, which may be related to previous selection on those populations.

Rapid Evolution of Multiple Species Increases Coexistence
Casey terHorst, Biology, California State University, Northridge
In this talk, community ecologist Dr. terHorst presented a model followed by empirical studies in a biological system on the topic of multispecies evolution in communities. The speaker first presented a model to combine the classic niche theory and neutral theory. These two theories seem to contradict each other, because one proposes a stabilizing mechanism for biodiversity, and the other proposes an equalizing mechanism. On the other hand, these two theories both propose ecological mechanisms instead of evolutionary mechanisms. The speaker presented models showing that evolution mediates coexistence in communities structured by exploitative or apparent competition. These mathematical results highlight how coexistence can be driven by a cyclic eco-genetic feedback similar to an extended rock-paper-scissor game, how evolution simultaneously can act as stabilizing and equalizing mechanism, and how rates of evolution impact the effectiveness of these mechanisms. The speaker then talked about population dynamics at the community level in a pitcher plant. Protozoa and mosquitoes compete within these communities. When individuals from different pitcher plant leaves (and hence different pool of communities) are put together to compete, it was observed that weak and strong competitors become strong and weaker and both end up as intermediate competitors.

TUESDAY, OCTOBER 8, 2013

The overlooked evolutionary dimension of modern fisheries
Ulf Dieckmann, Evolution and Ecology, International Institute for Applied Systems Analysis
Dr. Dieckmann began by discussing the collapse of the cod population (fishery) in the North Atlantic, setting the stage to discuss how fishing pressure and climate together affect population abundance and genetics. He also described how selection induced by fishing can affect population characteristics including maturation schedules, growth rates, reproductive investment, behavior, and morphology. After discussing key biological factors affecting fisheries – such as population structure, phenotypic plasticity, and tradeoffs between life-history traits – Dr. Dieckmann summarized the benefits and shortcomings of different modeling frameworks. Specifically, models that focus on maximizing reproduction (R_0 or r), models based on the Breeder's Equation, and Adaptive Dynamics models. He then detailed an eco-genetic model framework that tries to improve up on these existing frameworks for fisheries scientists and managers. These can be implemented as compartment-based ODE models or as individual-based models. Dr. Dieckmann then presented results for the dynamics of recovery from fishing to highlight the important role evolution can play in shaping those dynamics. He concluded with results for a set of "prototypes" (cod, anchovy, sharks and rays, and whales), each using data compiled for multiple species within each prototype group, to look across a range of fisheries types for common evolutionary responses to fishing (e.g. evolution tends to delay biomass recovery) and to identify prototypes that are most susceptible to overfishing.

Rapid evolution and species invasions

Emily Jones, Ecology and Evolutionary Biology, Rice University
Dr. Jones first discussed the high evolutionary potential that exists for species invading new habitats. This potential for evolution is driven by new selection pressures that arise from biotic and abiotic interactions in their new environment. She then discussed mechanisms affecting establishment: phenotype matching or mismatching with resident species, ecological responses, and evolutionary responses. Using a modified Lotka-Volterra model, Dr. Jones then presented results for how invader and resident evolutionary responses affect invader establishment, and described some management implications. The talk concluded with some discussion of open questions in this area, empirical information gaps related to resident-invader evolutionary dynamics, and the implications of this work for other cases of rapid evolution.

Algal Evolution in a Changing Ocean
Jeff Morris, Michigan State University
Dr. Morris began by discussing the important role marine ecosystems play, and the risks posed by human impacts like global warming and ocean acidification. Warming can influence growth and mortality rates, and lead to range restrictions. Acidification can increase Calcium Carbonate solubility, which risks stripping corals of their exoskeletons. Dr. Morris then focused on a the globally distributed unicellular marine cyanobacterium , *Prochlorococcus*, as an example where rapid evolution is likely to occur. After introducing his central scientific questions – how fast do mutations arise, how much do they affect algal fitness, and how will the dynamic ocean environment affect their dissemination in the population – Dr. Morris discussed how his lab and others are tackling these questions using a combination of experimental evolution techniques and global ocean modeling. One project will develop simulation models based on experimental data obtained by first evolving populations in the lab, then characterizing those evolutionary changes and any related tradeoffs and phenotypic plasticity. Dr. Morris concluded by presenting some preliminary simulation results using different species of marine algae, representative of the broad diversity within that group of organisms, and discussing future research directions.

Multiscale evolutionary dynamics: a measure-valued process perspective
Shishi Luo, Theoretical Biology and Biophysics, Los Alamos National Laboratory
Dr. Luo began by discussing the context in which pathogen evolution takes place, which includes selection within an infected host as well as selection in transmitting between hosts. Treating strains within hosts as a group, these multiscale processes can lead to conflicting selective pressures at the different scales. Dr. Luo then introduced an extension of the Moran model as a framework for such systems that includes stochasticity at each scale, but which can still be viewed as a "ball-and-urn" process. Dr. Luo presented the analysis of this model, namely that it converges weakly to the solution of an analytically tractable integro-partial differential equation, or to a set of ODEs under a different limit, which were used to infer other general properties of these multilevel selective forces.

Optimal control of pests in ecosystems
Suzanne Lenhart, Mathematics, University of Tennessee
Dr. Lenhart introduced the gypsy moth system, and the control aims of suppressing, slowing or even eradicating the invasive species from affected areas. For this talk Dr. Lenhart focused on

investigating the effectiveness of different management strategies, using optimal control but in an integrodifference equation framework. Results were presented that include top-down regulation from predation (by white-footed mice) and disease (nucleopolyhedrosis virus [NPV]), and compared those optimal control strategies to those from a model without top-down effects. Additional results were presented that investigated spraying NPV as an alternative to spraying insecticide for control purposes. This work involved control of explicitly spatial integrodifference equations that exhibited complex dynamics (i.e., host-parasite cycling similar to classical predator-prey cycles).

WEDNESDAY, OCTOBER 9, 2013

Fisheries-induced evolution and sustainable fisheries
Mikko Heino, Biology, University of Bergen
In this talk, the speaker talked about fishery-induced evolutions in fish stocks. The concern is that fishery strategies, such as size-dependent harvesting, may induce evolutions in the stocks that harm the populations. For example, models showed that harvesting large fish might induce a selection so fishes will tend to remain small. This is economically damaging, because bigger fish are economically more attractive. Other size- or age-dependent harvesting are also found to hurt the maximum sustainable yield. Even though fishery-induced evolution is found to be slow, so one may argue that it doesn't matter that much, the accumulation effect of such evolutions still matters. Harvesting medium sized fish is then sometimes found to be a better strategy.

Evolution as a stabilizing and equalizing mechanism
Sebastian Schreiber, Evolution and Ecology, University of California
In this talk, the speaker presented some recent research on possible stabilizing or equalizing mechanisms induced by evolution to maintain biodiversity. He considered two types of predator-prey modules: an "exploitative competition" module where a prey is shared by two predators, and an "apparent competition" where a predator preys upon two preys. The questions asked are: when does evolution at one tropic level stabilize and equalize competing species at another tropic level? What is the mechanism of stabilizing? And to what extent is the stabilization? The first two questions are answered by a clonal model. Simulations of an exploitative competition showed damped oscillations of prey trait evolvement (predator doesn't evolve) and predator populations. Eventually the prey evolves to an intermediate level against the predators. The mechanism of this stabilization can be though of as a "battle of sexes" game, which is similar to a rock-paper-scissors game but with an even number of equilibria (in this case, four equilibria). It was shown that the equilibria are all repelling and that is why there are heteroclinic cycles and coexistence. The third question is answered by a quantitative genetics model, and it was found that higher evolution rates strengthen the stabilization mechanism. Finally, analogous results hold for the "apparent competition" module.

The challenge of understanding antibiotic resistance
Odo Diekmann, Mathematics, Utrecht University
This talk was about antibiotic resistance in two contexts: those in the hospital and those in the animal production industry. The problem posed in the hospital context is that sometimes patients

are tested negative for the antibiotic resistant strain when admitted, but at some point during their stay they may test positive. The question is what happened during the hospital stay? There are two possible origins of the resistant bacteria: either the patient acquired it as a new infection, or it arose through mutation within the infected patient. The speaker then presented a Markov chain model of this process. In the animal production industry context, the concern is that small doses of antibiotics in agriculture may become big problems. There are several different mechanisms for that to possibly happen: mutation in chromosome, acquired plasmid carrying a gene, gene duplication or amplification, physiological adaptation, or persister cells. The speaker also presented an ODE system model that focused on physiological adaptation.

Historical DNA reveals dynamic patterns of recent microevolution in overfished populations of Atlantic cod

Nina Overgaard Therkildsen, Stanford University

Dr. Overgaard Therkildsen began by using Atlantic cod as an example of how fishing can impose selective pressures that lead to changes in how fish grow and mature. The first part of the talk addressed the question "Can we observe signatures of selection over decadal time scales in Atlantic code populations?" New genomic tools provide a means to better understand whether plasticity or evolution (or both) drive these changes, and the Atlantic Cod genome has been sequenced with dense coverage and large sample sizes. Using historical samples from across the species range, the genetic evidence is consistent with temperature (warming) and fisheries causing rapid selection on different parts of the Atlantic cod genome. More specifically, comparisons between different populations have revealed that the loci that showed high levels of differentiation over time ('outliers') were largely non-overlapping (i.e, population-specific) sets of loci. Outlier loci from an earlier period showed almost complete stability during later periods. The contrasting micro-evolutionary trajectories among populations resulted in sequential shifts among spatial outliers, with no locus maintaining elevated differentiation throughout the study period. These and other results suggest that population replacement or shifting migration patterns alone cannot explain the observed allele frequency variation, indicating that highly dynamic temporally and spatially varying selection has likely been important for shaping the observed patterns. These results shed light on how spatial and temporal biocomplexity can shape local evolutionary potential and adaptation, and underscore the need to account for those effects in fisheries management.

Eco-evolutionary feedbacks, adaptive dynamics, and evolutionary rescue theory

Regis Ferriere, Ecology & Evolutionary Biology, University of Arizona

Dr. Ferriere began with an historical overview of milestone papers tracing the history of studying eco-evolutionary dynamics, emphasizing the theoretical foundations for evolutionary rescue. Evolutionary dynamics can affect ecological properties (e.g., growth or consumption rates) at multiple levels, including at the level of the community or the ecosystem. Dr. Ferriere discussed other related phenomena - in particular, (co)evolutionary suicide and evolutionary trapping, whereby, in a changing environment, a population tracks a viable evolutionary attractor that leads to evolutionary suicide. Evolutionary trapping and suicide are commonly observed in adaptive dynamics models. Evolutionary rescue requires that the population overcome these evolutionary threats, thus evolutionary repellors play an important role in determining how environmental conditions affect evolutionary pathways that lead to rescue. In contrast with standard predictions

of evolutionary rescue theory, low genetic variation may attenuate the threat of evolutionary suicide, and small population sizes may facilitate escape from evolutionary traps.

THURSDAY, OCTOBER 10, 2013

Rapid evolution in the context of range expansion
Alex Perkins, University of California, Davis
In this talk, Dr. Perkins gave a brief survey of the well studied rapid evolution in ecology. Firstly, he talked about the unique aspects of rapid evolution in range expansion. Then he explained rapid evolution in range expansion. This often happens after many generations. And his work has documented evolution of range-expanding species, and is potential for impacting on order of known spread acceleration. After that, some mechanisms for rapid evaluation are given. Based on a reaction-diffusion equation, he explained the observed phenomena of front acceleration as well as other quantitative results, such as the selection of the most motile individuals. He also explained dispersal evolution by spatial sorting and spatial selection for different dispersers. Dispersal evolution can be applied to model life history. Finally, he explained the results of his model comparing with the experiment data with different aspects and provides some prediction versus observation.

Streamlining Theory in Microbial Evolution
Stephen Giovannoni, Microbiology, Oregon State University

Dr. Giovannoni first presented the idea of streamlining theory: genome size is inversely related to effective population size (Ne). Then he explained that streamlining theory attributes small cells and genomes to selection for the efficient use of nutrient resources in populations where Ne is large and nutrients limit growth. He showed some results and discovered that small and abundant cosmopolitan marine bacteria with small genomes led directly to streamlining theory. Then he talked about the small genomes of bacterioplankton, which were interpreted as streamlining, namely, cases of extreme selection reducing unessential structures and producing minimized cells. He also presented the result of the minimal characteristics of streamlined marine bacteria, which are attributed to large population sizes and selection favoring the efficient use of limiting resources. Finally, he proposed that this idea might apply broadly to other microbial ecosystems, such as Black Queen Hypothesis, SAR11, and ocean warming.

International agreements for optimal disease control
Petra Klepac, Mathematics and Theoretical Physics, University of Cambridge
Dr. Klepac started with the smallpox eradication for three diseases: polio, guinea worm and yaws, and then proposed a question: what are optimal levels of control in the face of evolutionary risks? Then she showed the different levels for design of effective control strategies: individual level, population level and regional level. So the question is transferred to be determining optimal level of vaccination under economic constraints requires integrating economic and epidemiological dynamics into a unified framework. She claimed that optimal coverage lies anywhere from no intervention to elimination depending on the severity of the disease and relative costs of infection and vaccination, and that achieving the optimal level of

vaccination depends on whether enough individuals get vaccinated. Individual behavior is difficult to estimate, and her results showed that individual incentives to get vaccinated decrease when the population is increased. Then she switched to the interplay of economic factors on multiple levels, and used the SIR model to describe the spatial coupling through movement of infected and international cooperation. Her results show that optimal strategy does not necessarily result in equitable vaccination coverage. She used the Lubombo regional malaria control collaboration as an example of successful coalition of institutions functioning as a regional public health tool.

Rapid evolution of dispersal and the bioeconomic optimality of marine reserves
Mike Neubert, Biology, Woods Hole Oceanographic Institution
Dr. Neubert began his talk with the tradeoff between efficiency rent and participation employment, and proposed a simple spatial Gordon model with equilibrium revenue and cost. Two problems are derived based on this model: open access for rent dissipation and rent density; and social optimum: an optimal problem for low cost. He then talked about the distribution of cod fish when a finite number of non-cooperating states exploit a shared mobile stock, and proposed a Nash equilibrium, namely, no harvester can do better by unilaterally changing his or her effort. Aggregate results were shown, and demonstrated that marine reserves are economically optimal when dispersal evolves. Then he switched to a "chalk talk" to explain the model and the PDE system being employed.

Feedbacks between ecology and evolution in Trinidadian Guppies: linking theoretical models with empirical research
Ron Bassar, Environmental Conservation, University of Massachusetts
This speaker began with the definition of an eco-evolutionary feedback by using a heuristic model, and proposed three questions: What is an eco-evolutionary feedback? Are they important to ecological and evolutionary dynamics? Can they be used to explain natural phenomena life history evolution in guppies? In his model, he assumed that evolution can influence population dynamics and fitness depends on the ecological state of the system (population density) and frequency-dependent selection. He claimed that eco-evolutionary feedbacks are the realization that fitness should be determined explicitly from the within and between population feedback structure. Then he showed a heuristic model as an example that these types of eco-evolutionary interactions are important in explaining life history evolution in Trinidadian guppies. He also compared the result of this mathematical model with experimental mesocosms, and explained which trait values evolve.

FRIDAY, OCTOBER 11, 2013

The eco-evolutionary dynamics of predator-prey systems: How does (co)evolution alter community level population dynamics?
Michael Cortez, Biology, Georgia Institute of Technology
This speaker started with an example to demonstrate that rapid evolution alters rotifer-algae cycles, and asked the question: how does evolution affect predator-prey dynamics? He then presented his eco-evolutionary predator-prey model, which includes total prey density, total predator density,

average prey trait, and average predator trait. Then he explained how to understand mechanisms via fast evolution: dynamics decompose into slow ecological dynamics and fast evolutionary dynamics. He also pointed out that prey or predator evolution can also drive cryptic cycles, and that fast evolution predicts costs for defense and offense. After that, examples of cryptic phage-bacteria cycles and mink-muskrat cycles were given to demonstrate predictions posited by his theory. Finally, Dr. Cortez concluded by answering his initial question: evolution leads to changes in the relative timing and ordering of population peaks, and changes in cycle shape in the phase plane.

Optimal control of models to sustain populations
Wandi Ding, Mathematical Sciences, Middle Tennessee State University
Dr. Ding talked about optimal control applied to the systems of PDEs, ODEs, and difference equations. She first presented a model of native-invasive population dynamics (cottonwood and salt cedar) based on ODEs. In this model, they want to maximize the native species at final time subject to balancing the minimization of the invasive species and the cost to implement the control. She then gave a proof of existence of an optimal control: uniqueness of solutions to the optimality system will imply uniqueness of optimal control. Numerical simulation was used to demonstrate this optimal control procedure. Then she switched to the optimal harvesting of fisheries to demonstrate Pontryagin's maximum principle by using the optimal control. Numerical simulations were used to show the optimal harvesting. She finished by talking about the application of the optimal control on non-timber forest product.

Current Topic Workshop: Mathematics Guiding Bioartificial Heart Valve Design

October 28-31, 2013
Organizers: Suncica Canic (University of Houston), Boyce Griffith (New York University), Aresh Kheradvar (University of California, Irvine), Stephen Little (Houston Methodist Hospital)
Report by: Kimberly Fessel, Jay Newby, and Michał Seweryn

MONDAY, OCTOBER 28, 2013

100% reparability in the mitral valve
Gerald Lawrie (Cardiovascular Surgery, Baylor College of Medicine)
Dr. Lawrie began the conference by offering a surgical perspective of the considerations and complications in cardiac mitral value reconstruction. He presented several images to introduce the anatomy of the mitral value including its leaflets, its annulus, and its proximity to other cardiac apparatuses. Healthy mitral value functionality requires multicomponent cooperation; for example, aortic-mitral coupling can be described as a loop process and results in rocking motion. Dr. Lawrie noted that not only the area but also the concavity/convexity map of the mitral valve is important in cardiac health and that patients with a "floppy" mitral value experience cardiac complications in a disease state. To restore heart health, surgeons attempt to reduce the size of the mitral annulus by inserting a ring around the valve. If a rigid prosthetic ring is inserted, however, the stress within the value is too great. Dr. Lawrie suggests that a flexible ring should be used

instead in order to restore the three-dimensional geometry as well as the appropriate strains within the valve.

Aortic valve modeling in 3D and 0D
Raoul van Loon (College of Engineering, Swansea University)
Dr. van Loon presented a computational model for the fluid-solid interaction between the aortic valve and its surrounding blood. After noting the general assumptions of his model, Dr. van Loon introduced several types of finite element methods that can be used to solve the system including Arbitrary Lagrangian-Eulerian (ALE), fictitious domain (immersed boundary), and ALE with remeshing. He also mentioned that because the fictitious domain method does a poor job near the boundary of the solid, adaptive meshing should be implemented in a small region around the valve. Dr. van Loon offered several example cases to compare these computational techniques and discovered that, overall, both ALE and fictitious domain with adaptive meshing perform well. When extending these methods to three dimensions, one must characterize the valve geometry. It may be possible in the future to use patient-specific parameters for this description to achieve personalized medicine. Dr. van Loon concluded with some of his recent work on lumped parameter models, which he uses to optimize treatment strategies in patients with multiple cardiac diseases.

The aortic root: Challenges in re-creating nature
Abe DeAnda (Cardiothoracic Surgery, New York University)
The aortic root involves several jointly operating structures in which geometry is intimately connected to functionality. Furthermore, several cardiac valve diseases can be classified as geometric irregularities. Dr. DeAnda offered a surgical point-of-view about aortic repair as well as several a priori surgical considerations. For example, valve conformational changes are likely caused by not only pressure differentials but also redistribution of loading shear stress. He briefly reviewed the history of aortic repair and mentioned that the greatest inadequacy of artificial valve replacements is the inevitable reduction in valve flexibility. Though many aortic repair options exist, none are completely satisfactory. Dr. DeAnda closed by posing design standards for the ideal aortic repair surgery: procedural simplicity, no post-operative anticoagulants, restoration of proper aortic wall stresses, and durable, natural materials for the valve replacements.

Multiscale modeling of the mitral value
Michael Sacks (Biomedical Engineering/ICES, University of Texas)
Mitral value repairs often result in better patient outcomes than valve replacements. Suspecting artificial valve material deficiencies, Dr. Sacks seeks to understand this phenomenon by researching the multiple layers that comprise mitral valve tissue. Tissue stresses and strains are particularly important for the valve, and Dr. Sacks presented his cellular deformation simulations that focus on using a finite element method to couple organ, tissue, and cell effects. Dr. Sacks works intimately with experimental labs to study mitral leaflet fiber kinematics. In his experience, including the fibril properties and representing the mitral valve as a viscoelastic material has a dramatic effect on his partial differential equations model and is therefore critical for further modeling efforts. Dr. Sacks also briefly highlighted a three-dimensional multiscale model for replicating the effects of contraction on the valve tissue.

Transcatheter heart valve design: Textile as an alternative to biological tissue?
Frédéric Heim (Research & Development, Université de Haute-Alsace)
Presently, only the most critical patients are implanted with transcatheter valves, but with modern improvements this technique may be extended to less severe patients, further increasing the need for long-lasting valve materials. The fragility of the biological tissue used in present-day valves limits these artificial replacements. Deliberately engineered textiles could be a candidate for future transcatheter valves due to their low stiffness, high resistance, favorable folding characteristics, and low risk of catastrophic structure failure. Dr. Heim explained that many parameters may be adjusted to develop the optimal valve textile, and he has found that, in particular, thinner textiles are more flexible and have less incidence of regurgitation. Dr. Heim then discussed some of the results of his valve fatigue tests, crimping tests, as well as his *in vivo* experimentation with textile valves for sheep subjects; all of which have been promising though much more work on textile optimization needs to be done.

Patient specific simulations of native and prosthetic heart valves
Anvar Gilmanov (College of Science and Engineering, University of Minnesota)
Methods for image guided, patient specific simulations contribute significantly to optimization of valve implementation. Dr. Gilmanov introduced a computational model of fluid-structure interaction for tri-leaflet valve at aortic position. Motion of the valve was partially reconstructed (i.e. a boundary condition) by an MRI based imaging technique. Simulations for the model were based on finite element structure solver. Dr. Gilmanov presented detailed results of simulations and discussed challenges of such approach. As a further direction he has proposed a similar framework for simulation of stent behavior.

Experimental platforms for validating computational approaches to simulating heart valve flows
Ajit Yoganathan (Biomedical Engineering, Georgia Institute of Technology)
Currently much effort is placed on integrating experimental design and computational modeling for implementation and performance of cardiovascular devices. Basic issues addressed here are durability of the device, its influence on hydrodynamics and the solid mechanics of the valve itself. Dr. Yoganathan first presented a heuristic, patient specific model and discussed the role and challenges of numerical simulation in such setting. Then a physical, mechanistic left heart model was introduced together with methods for recreating (by ultrasound or micro-CT) the geometry of the valve and issues related to hemodynamics. Such simulators were used to generate datasets for the flow through the mitral valve, movement of the leaflets and subvalvular force measurements. According to Dr. Yoganathan, future challenges include modeling of transcatheter aortic valve replacement and the effect of positioning the valve on hydrodynamics and solid mechanics of the device.

Developing a mechanically biomimetic hydrogel scaffold for heart valve tissue engineering
Jane Grande-Allen (Bioengineering, Rice University)
Constructing an artificial heart valve is a major challenge not only from a mechanistic, but also a biochemical point of view as far as engineering appropriate materials is concerned. The current

strategy is to use polymer hydrogels for engineering the device of interest. Dr. Grande-Allen discussed challenges related with engineering tissues as well as results of experiments with different hydrogels. A detailed presentation of predictive models for pattern formation in hydrogels was also made. Among these the Itzhakov-type model represents nonlinearity of hydrogel tensile fairy well, whereas the Holzapfel-Gasser-Ogden model is most straightforward to use. Dr. Grande-Allen showed results of experiments on micro-patterns, their influence on modulation of cell morphology and development of laminated hydrogels.

TUESDAY, OCTOBER 29, 2013

Time for AVR...Calculating Risk
Stephen Little (Cardiovascular Imaging Section, Department of Cardiology, Houston Methodist Hospital)
Dr. Little's principal area of research is in valvular disease, particularly, the mitral valve. He has developed an in vitro model of mitral regurgitation that allows three-dimensional assessment of regurgitant flows. His long term aim is to develop a robust methodology for quantification of severity of mitral regurgitation that can be applied clinically, and improve on current methodology.

Cell-mediated retraction and remodeling in engineered cardiovascular tissues
Frank Baaijens (Biomedical Engineering, Eindhoven University of Technology)

Preclinical studies of tissue-engineered heart valves show retraction of the heart valve leaflets as major failure of function. This retraction is caused by both passive and active cell stress and passive matrix stress. Cell-mediated retraction induces leaflet shortening that may be counteracted by the hemodynamic loading of the leaflets during diastole. To get insight into this stress balance, the amount and duration of stress generation in engineered heart valve tissue and the stress imposed by physiological hemodynamic loading must be quantified.

Percutaneous Heart Valve from bench to bedside
David Paniagua (Baptist Hospital and Biomedical Engineering, Florida International University and Kendal Medical Center)
The endeavor to create a percutaneous aortic valve dates back to 1965. Several researchers have tried to develop this project since that time. The speaker's group started working on the development of a percutaneous heart valve for human use in early 1998. They implanted the first percutaneous heart valve in animals in June of 2000 in Costa Rica. They have tested this newly designed valve for almost 2 years in a chronic in vitro testing model that consists of a closed circuit of plastic tubing connected to a reservoir and a pulsatile diaphragmatic pump (flow rates from 1 to 5 gallons per minute) that mimics the heart function.

A pulsatile in vitro heart valve model utilizing multi-modality imaging for assessment of transvalvular flow and velocity fields
Matt Jackson (Cardiovascular Hemodynamics Imaging Laboratory, The Methodist DeBakey Heart and Vascular Center)

Dr. Jackson has evaluated and compared the fluid dynamics at the anastomosis created by a hybrid vascular graft to the conventional end-to-side anastomosis created by a conventional arteriovenous graft. The in vitro study was performed using an MRI-compatible mock circulation. He used phase-contrast MRI in conjunction with computational fluid dynamics. The hybrid vascular graft eliminated the low wall shear stress region at the toe and the heel of the graft anastomosis site, which corresponds to the development of intimal hyperplasia in the conventional end-to-side anastomosis.

Measure of Asymmetry of Transmitral Vortex Ring
Arash Kheradvar (Biomedical Engineering, University of California, Irvine)
Color doppler imaging is a tool to obtain intracardiac flow information and considers only a single component of velocity along the transducer scan line and does not provide quantitative information with respect to vortex formation, recirculation areas, and flow stagnation zones. Because of these limitations, color doppler imaging may not provide adequate information for either the reconstruction of velocity vector fields or the actual direction of streamlines. Quantitative PIV-enabled echocardiography technique is an ultrasound, non-doppler, method to measure multi-component velocity information non-invasively. This method is the in vivo equivalent of optical particle image velocimetry techniques and is named echo-PIV. Once particles are detected within the flow field, particle image velocimetry algorithms can be applied to determine the local velocity vector.

Completely-biological Tissue-engineered Heart Valves Based on Predictable Cell Induced Contraction and Alignment of Biopolymers
Robert Tranquillo (Biomedical Engineering, University of Minnesota)
The more complicated geometry and mechanical function related to leaflet bending for valve opening and closing poses new challenges to relate optimal mold design to ultimate function of the valve-equivalent. Dr. Tranquillo is developing a novel controlled-stretch bioreactor and use of photo-crosslinked fibrin as complementary strategies to achieve greater bending stiffness and strength of the valve leaflets. He seeks to generate a myocardium-equivalent, or heart patch, by exploiting the contact guidance features of tissue-equivalent fabrication to attain requisite electro-mechanical function. A distinctive feature of this heart patch is creating a self-assembled network of dense and aligned microvessels that allows for efficient nutrient transport.

A Fluid-Structure Interaction Model to Simulate Mitral Valve Regurgitant Flow
Annalisa Quaini (Mathematics, University of Houston)
Numerical approximation of fluid-structure interaction problems is a particular concern with hemodynamics applications. To solve the coupled problem, Dr. Quaini uses new semi-implicit algorithms based on inexact block-LU factorization of the linear system obtained after the space-time discretization and linearization of the FSI problem. As a result, the fluid velocity is computed separately from the coupled pressure-structure velocity system at each iteration, hence reducing the computational cost. The algorithms derived from inexact factorization methods are compared with other schemes based on two preconditioners for the FSI system: Dirichlet-Neumann preconditioner and an ILUT preconditioned combined with a suitable diagonal scaling. All the methods are tested on two and three-dimensional blood-vessel systems. The structure model is

improved by representing the vessel wall as a linear poroelastic medium. All the FSI algorithms apply to fluid-poroelastic structure interactions. Their numerical performance compared well on simplified blood-vessel systems.

WEDNESDAY, OCTOBER 30, 2013

Mechanobiology of aortic valve biology and disease

Craig Simmons (Mechanical and Industrial Engineering, University of Toronto)

Dr. Simmons opened his talk with a background on the biology of heart valve calcification. Deregulation of fibroblasts, spatial predictions of pattern formation and interactions with microenvironment were emphasized to be crucial factors in disease description. Here, of particular interest is the signaling mechanism through cytokine secretion (such as TGF-beta), local expression of cytokines and protective mechanism (against fibrosis) of the C-type natriuretic peptide. Dr. Simmons stated the main modeling question on how the stiffness of the extracellular matrix influences fibrosis of valvular interstitial cells. Cellular output was modeled as a function of the extracellular matrix stiffness input. In the experimental setting, it was assumed that fibrosis is driven by TGF-beta and other microenviromental factors. Presented results suggest that on extracellular matrices with stiffness above a certain threshold cells do not experience calcification.

Multiscale Models of the Aortic Valve Mechanics

Mohammad R.K. Mofrad (Bioengineering and Mechanical Engineering, University of California)

The most common disease of the aortic valve is calcific aortic stenosis, therefore multiscale models of the disease are of great significance. Dr. Mofrad began with a description of the aortic valve form a mechanistic point of view and followed by the discussion on issues with integrating organ-scale and cell-scale modeling approach. He first presented the organ-scale model together with a validation technique, then he moved on to introduce a tissue-scale model for leaflet movement modeling and finally a cell-scale model was presented with appropriate boundary conditions. As a continuation a model for calcific aortic stenosis was introduced, which incorporates a multiscale approach and attempts to explain the process of valve aging. Next, Dr. Mofrad used a mechanistic approach to look at differences between bypassed versus a normal valve. He then discussed a molecular framework on how the cell senses signals form the matrix and what is the role of transcription factors (and their geometry) in the process.

Patient specific multiscale modeling in pediatric cardiology

Alison Marsden (Mechanical and Aerospace Engineering, University of California, San Diego)

Dr. Marsden began her talk by reviewing the medical benefits of computational modeling. Besides surgical planning, numerical simulations may also be used to test new, radical procedures, design patient-specific implants, predict post-operative conditions, and stratify risk among various surgical options. Dr. Marsden then described a numerical formulation which couples a patient-specific 3D heart model to a 0D lumped parameter model for the remainder of the circulatory system. This 0D representation is based on a circuit network, and its results are used as the cardiac inflow/outflow boundary conditions. Dr. Marsden explained that she uses this type of framework

to evaluate the merits of competing surgical techniques by altering the system geometry in a mimicking "virtual surgery." The model reproduces not only the 3D velocity and pressure fields but also the global parameters, which characterize many physiological quantities of interest to clinicians. Case-specific "virtual surgeries" can be performed with the model to inform an individual patient's surgical choices; furthermore, new procedures can be analyzed before being tried on an actual subject.

Mathematical modeling of endovascular stents
Suncica Canic (Mathematics, University of Houston)
A variety of stents are available to strengthen weak or narrow human blood vessels. To choose the correct type for the task at hand, one must carefully consider the global properties of the stent, such as its response to radial compression or bending. These global characteristics are largely defined by the local properties of the stent's struts. In general, numerically representing these small-scale features under external loading in three dimensions requires a very fine mesh and is computationally expensive. Dr. Canic proposed an alternative one-dimensional approach, which makes use of strut symmetry. She presented the system equations and then compared the results of the 1D and 3D computations. While both methods produced similar outcomes, the 1D method required significantly less computation time. Dr. Canic ended by suggesting that her model be used to evaluate new stent designs and to eventually optimize artery-specific manufacturing.

Computational modeling of drug eluting stents
Paolo Zunino (Mechanical Engineering and Materials Science, University of Pittsburgh)
A drug eluting stent (DES) is a small mesh tube that is permanently inserted in a partially obstructed artery both to restore the vessel's diameter and to locally release a drug at a controlled rate. Modeling the time evolution of the stent's effects requires careful consideration and challenging computational analysis. Dr. Zunino explained his DES representation, which accounts for various blood flow regimes, fluid-solid interactions, transport through the porous media, and multiple scales. To reduce the complexity of the model, Dr. Zunino has considered the vascular geometry as well as an immersed finite element framework. He then demonstrated an example application of his method in a coronary bifurcation artery and noted that stent geometry plays an important role in drug distribution.

Inverse problems in Cardiovascular Mathematics: from simulations to assimilations
Alessandro Veneziani, (Mathematics and Computer Science, Emory University)
Integration of numerical simulations and noisy measurements is a major challenge when introducing mathematical and numerical models as a tool used by physicians in the decision making process. The goal is to find an appropriate mathematical model to fill the gap of lack of data in cardiovascular designs. Dr. Veneziani introduced basic concepts of his modeling approach, which is based on solving inverse problems (variational problems and/or Kalman filtering). A bidomain model for electrocardiology was introduced and a theorem on existence of a solution based on Tikhonov regularization was presented together with various simulation results. The second example of application of inverse problems to cardiovascular design was related to evaluation of arterial compliance. Next, Dr. Veneziani discussed issues related with reducing

computational costs by reducing the dimension of the model, as well as reducing the solution by a singular value decomposition-type technique.

Use of Reverse Finite Element Analysis to Determine Mitral Valve Stiffness in the Beating Heart
Julia Swanson, (Thoracic & Cardiovascular Surgery, University of Virginia)
Dr. Swanson opened her talk with a detailed description of the experimental methods that have been successfully used for a number of years in her lab to answer questions related to geometry of the leaflets in the beating heart. The two crucial questions are: Why is there a characteristic curvature of the leaflets and what drives the stiffness of the leaflets? Two features that have direct impact on stiffness of the leaflets are shape and morphology. As far as the first one is concerned, Dr. Swanson presented how an appropriate model together with a finite element analysis approach may be applied to model the shape of the leaflet. It was also noted that the stiffness of leaflets is larger in a beating heart then in in vitro experiments. Therefore a natural question arises what is this phenomenon driven by? From various experimental designs it was concluded that stiffness remains the same in different phases of the heartbeat, also neuro-stimulation does not change the stiffness and what is more, beta-blockers reduce stiffness only in one phase of the cycle. Therefore Dr. Swanson concluded that it is the cardiac muscle that drives stiffness in a beating heart, whereas the smooth muscle sets the pace for the leaflet movements.

Immediate and Delayed Effects of Stent Crimping on Transcatheter Valves
Elliott Groves, (Cardiology, University of California, Irvine)
Even though transcatheter aortic valve replacement is a procedure used successfully in patients with severe aortic stenosis, there is a lack of evidence on how stent crimping influences the performance of the device. Dr. Groves has addressed this question in his talk. He began with introducing a model of a heart valve engineered in his lab and discussed the relation of this device to other types of valves used by physicians. The experimental design was as follows: Tissue was crimped at the depth of 14, 16 and 18 French-catheter and scanned by electron microscopy immediately, after 20 minutes and after 60 minutes. Results of these experiments (images) were analyzed in Matlab and a ‘damage index’ was proposed as an appropriate measure of the tissue destruction. Dr. Groves noted that significant structural damages induced by crimping may lead to early mechanical failure of the device, early calcification and may cause more susceptibility to thrombosis. As a further perspective an improvement of the ‘damage index’ was proposed together with integration of this index with histological analysis.

THURSDAY, OCTOBER 31, 2013

Sub-Kolmogorov turbulence in heart valve flows: Theory to predict distribution of viscous shear stress on blood cells
Lakshmi Prasad Dasi (Mechanical Engineering, Colorado State University)
Patients receiving prosthetic heart valves are required to take anticoagulant drugs for the remainder of their lives because, as Dr. Dasi explained, increased shear stresses near the artificial valve damage blood cells and result in higher clotting risk. Dr. Dasi seeks to characterize blood flow patterns in valve regions via computational simulations. Numerically calculating viscous shear stresses within the heart is quite difficult. One could look at Reynolds stresses instead; though,

Dr. Dasi cautioned that neither type gives a complete picture of post-operative blood cell damages. In his talk, Dr. Dasi suggested that shear stresses calculated from local energy dissipations are the best predictors, and he further verified his energy balance approach by comparing his unified model with experimental data from both laminar and turbulent flows.

Scaling effects during heart valve development
Laura Miller (Mathematics, University of North Carolina)
In her presentation, Dr. Miller focused on vertebrate cardiogenesis; in particular, she discussed how the fluid flow—and perturbations to this flow—influences embryonic heart development. Because viscous effects dominate low-Reynolds-number systems and inertial effects prevail in flows with high Reynolds number, profound variation is observed in flow patterns for Reynolds number ranging between 1 and 100. Dr. Miller explained that animal hearts experience a transition in this regime during initial development, and she reviewed the results of both experimental and mathematical tests for systems with varying Reynolds numbers. She concluded by asserting that these changes in embryonic fluid dynamics could be important in overall cardiac anatomy and functionality formation.

Modeling cardiac fluid-structure interaction
Boyce Griffith (Medicine, New York University)
Because of the dynamic interplay between the heart valves and the surrounding blood, numerical simulations for cardiac systems require serious thought about fluid-solid interactions. Dr. Griffith opened his talk by explaining the immersed boundary method, which he uses in his computational setup. He then showed several movies of his patient-specific results, which simulate a beating human heart. Dr. Griffith also presented an extension of his work to a detailed model of blood flowing through the aortic valve leaflets. For this representation, he makes use of a Lagrangian finite elements scheme to translate his partial differential equations into the immersed boundary framework. His qualitative outcomes match biological expectations, and he further remarked that he is currently validating his results quantitatively using a rigid prosthetic valve model.

Modeling Platelet Deposition and Coagulation under Flow: Transport of Platelets and Proteins to and within the Thrombus
Aaron Fogelson, (Mathematics, University of Utah)
Dr. Fogelson began his talk with some background on the process of thrombosis and earlier work on its modeling. From a mechanistic point of view formation of a thrombus is initiated with disruption of the endothelial layer, whereas form microbiological point of view the key role is played by an enzyme – thrombin – and is heavily dependent on the way that proteins are transported within the blood vessel, but also within the thrombus itself. The first model presented by Dr. Fogelson's included terms related to fluid dynamics, cell accumulation and cell-to-cell interactions and a cascade for enzyme amplification. The underlying assumption is that the environment is homogenous and molecules are well mixed. Yet to capture the dual role of platelets a more complex spatial-temporal modeling approach is needed, which incorporates not only heterogeneity of the environment and physical inhibition by platelets, but also protein transport within the cloth. Dr. Fogelson concluded his talk by presenting simulation results for the model,

which show that the spatial disconnection between the substrate and the enzyme prevents the cloth from overgrowing.

Autumn Emphasis Semester Workshop 3: Sustainable Management of Living Natural Resources

November 4-8, 2013
Organizers: Paul Armsworth (University of Tennessee, Knoxville), Alan Hastings (University of California, Davis), and Andrew Liebhold (USDA Forest Service)
Report by: Noelle Beckman, Karly Jacobsen, Michal Seweryn

MONDAY, NOVEMBER 4, 2013

Big picture and charge
Challenges in the management of natural systems
Alan Hastings (University of California, Davis)
Dr. Hastings opened the workshop with a broad discussion of the challenges of formulating tractable models in problems pertaining to the management of natural systems while including sufficient complexity. He delineated the many typical assumptions, utilizing the example of a basic bioeconomic fishery model, and emphasized the need to carefully consider these assumptions, alternate approaches and their inherent mathematical limitations. He further framed the goal for the workshop to be to determine what mathematical challenges there are for increasing complexity of models, such as through incorporation of spatial and genetic structure, multispecies and human behavior interactions, and environmental and demographic stochasticity, and to find appropriate solutions. Dr. Hastings illustrated the critical importance of a multispecies approach with his work on trophic cascade affects occurring in marine reserves where he concluded that release from fishing pressure even for a bycatch species has a greater impact than increased predation.

Regional natural resource management: Comments on optimization, control, feasibility, and future directions
Lou Gross (University of Tennessee, Knoxville)
Dr. Gross continued the discussion of challenges and feasibility of mathematical models for optimization in natural resource management, focusing on model objectives, criteria for evaluation, and varied interests among multiple stakeholders. To assess the dynamic impacts of alternative hydrologic management planning in the Everglades, Dr. Gross and colleagues developed a multimodel, Across Trophic Level System Simulations (ATLSS). ATLSS integrates agent-based, age- and size-structured, process and spatially-explicit species index models to provide a scenario ranking analysis. In addition, Dr. Gross addressed an optimal spatial vaccination strategy for a multi-patch rabies model for the eastern United States as well as development of a model to optimize wildfire. This is novel in its feasibility to be used for real-time analysis in the field due to supercomputer preprocessing. He concluded with further discussion of the need to address challenges at the interface of mathematics and sustainability including determining what resolution of agents are essential to capture diverse components,

formulating general guidance for when scenario rankings are robust to uncertainties, incorporating multiscale aspects and evaluating robustness of spatially-connected economic and environmental models.

TUESDAY, NOVEMBER 5, 2013

Conservation planning and ecosystem services

"Buying" conservation benefits form private landowners

Paul Armsworth (University of Tennessee)

Dr. Armsworth opened his talk with the subject of integrating Ecology and Economics, by giving the context of payments made by agencies to landowners and also presenting some further directions in this area. In what followed Dr. Armsworth discussed challenges in modeling human-nature interactions and also explained the basic assumptions of the modeling approach. Within the game-theoretic setting, both continuous and discrete conservation investment models were presented together with assumptions on the landowners' decision function. Results for the Nash equilibrium for such systems were presented, where parameter values were taken from previous studies of 44 livestock farms. Next, Dr. Armsworth discussed details and results related to uncertainty analysis (incomplete information). In such case landowners tend to bias their prices upward, which results in loss of biodiversity. The last of the presented models was 'discrete benefits–discrete controls' model in which farmers are allowed to collaborate together with solutions on the "worst case scenario". It was concluded that in the case of such "auction scenario" landowners tend benefit less then in the continuous model.

Spatial planning for ecosystem services and/or biodiversity benefit metrics

Hugh Possingham (University of Queensland)

Dr. Possingham discussed systematic marine reserve design as an improvement on the pseudo-quantitative tools currently used in conservation planning. While greedy algorithms are inadequate to solve large-scale problems such as design for the Great Barrier Reef Marine Park, Marxan software, developed by Dr. Possingham and colleagues, can find a solution minimizing cost by utilizing a simulated annealing solution method. In addition, Dr. Possingham considered a dynamic ordinary differential equations system to determine an investment plan for global biodiversity, in particular for forest and bird species richness in Pan Malaysia, Borneo, and Sumatra. The slope of the resultant species-money curve quantifies return on investment and therefore can be used to decide where to spend money to minimize loss of biodiversity. Finally, Dr. Possingham emphasized that only static, one-step optimization methods are used in practice and that simplicity is crucial in delivery to policymakers in order to make an impact in biodiversity conservation.

Linking individual movements and population patterns in dynamic landscapes

Bill Fagan (University of Maryland)

Dr. Fagan discussed micro to macro scaling in population-level movement patterns, modeling spatial memory in animal movement and the identification of movement modes in the analysis of real animal movements. The effectiveness of alternative movement mechanisms, including oriented, non-oriented and spatial memory, can lead to different emergent population-level distribution patterns such as range residency, migration and nomadism. A comparison of spatial-

temporal habitat complexity vs. net fitness benefit yielded the result that memory is most useful in the presence of intermediate levels of habitat complexity. He outlined the statistical signatures of memory-based movement including homing, searching, territoriality and migration. Dr. Fagan also illustrated the link between social learning and migratory performance in a study of whooping cranes. In analyzing more complex movement modes with problems of sampling dependence and blindness to non-Markovian effects, Dr. Fagan and colleagues have had success expressing movement models via semi-variance functions. This method allowed identification of a three-part model for the movement of mongolian gazelles which was consistent with data across all time scales.

WEDNESDAY, NOVEMBER 6, 2013

Invasives and disease

Managing Bioinvasions: where, when, who and how much?

Rebecca Epanchin-Niell (Resources for the Future)

Dr. Epanchin-Niell began her talk by presenting interesting examples of models in which characteristics of the landscape are an important factor in the spread and persistence of invasive species, which results in loss of biodiversity. One such example is related to policy of early detection of new invasions in New Zeeland, where detailed discussions were made on cost vs. tradeoff of such approach. In this context, a bioeconomical model was presented in which many economical and environmental factors were taken into account (such as sampling intensity – density of traps) and the management cost is being optimized. She followed with a framework for optimal spatial control strategy that includes optimal control of established invasions as well as modeling of the spread of invasion (sampling strategy). This model consists of a diffusion process, environmental heterogeneity term, biodiversity adjustment and correction for spatial geometry (a SIS model with a grid). The control options are either to prevent the spread or to eliminate the invasion, and the strategy with the optimal cost-damage ratio is chosen. The solution follows from the application of integer programing methods. Dr. Epanchin-Niell closed her talk with a detailed discussion of issues related to cooperative management of invasive species. In this setting three bottom-up types of cooperation were introduced and results were presented.

Disturbance, diversity and invasion ecology

Katriona Shea (Pennsylvania State University)

Dr. Shea discussed detailed relations between diversity and disturbance in biological systems. At the beginning emphasis was placed on the definition of disturbance itself and association of disturbance with invasions. First, the concept that intermediate disturbance allows for high biodiversity was reviewed. It was then noted that reported results on relation between diversity and disturbance are inconsistent; thus there is a need for theoretical studies in this subject. Dr. Shea presented a model for two annual plants, together with a detailed analysis of the predictions that describes all possible patters of association between diversity and disturbance. Next, crucial features of disturbance were discussed, these include: frequency, intensity, extent, duration, timing, and pace. In the analysis of the impact of these features, it was inferred that high intensity disturbance improves management, and when timing is included, frequency of disturbance is not important. If autocorrelation of disturbances is then introduced, it was noted that changing the autocorrelation may alter the results completely. As further extensions, Dr. Shea briefly discussed

impact of climate change on invasive species, perturbations of theoretical and empirical biological networks, and experiments on disturbance in population of microorganisms.

Data, uncertainty and risk in biological invasions
Brian Leung (McGill University)
Dr. Leung discussed current approaches to comprehensive risk analysis. General challenges include the limitations in time, information and resources. Risk related to invasions was defined as the expected severity impact of the invasion – that is, the probability of the invasion times the impact of the invasion. Models for risk assessment predominantly apply to a single species (these include both scoring and quantitative approaches) with roughly 4% of models being built for multiple species or pathways. It was noted that scoring approaches are largely underdeveloped, whereas the more popular quantitative approaches use well-known statistical tools as Bayesian or sensitivity analysis. Dr. Leung presented TEASI, a framework for building risk assessment models for biological invasions. Individual components of the framework were presented together with examples of invasions in Lake Michigan. Model validation was performed by comparison of the long-term forecast with the current state. Next, the model was adapted to multiple species setting. In such case it is of interest to predict which species is at most risk. Both the propagule pressure model and the joint model performed well in realistic simulation studies. At the pathway level a risk management model related to forest insect pests was presented together with empirical results and forecast.

Vector Dynamics and Disease Control
Michael Bonsall (University of Oxford)
In his talk, Dr. Bonsall discussed ecological, epidemiological, and economical aspects of disease control by vector-based methods. The presentation was divided into four parts: vector biology, ecological dynamics of vector control, vector control and disease economics, and vector control and human movement. As far as vector biology is concerned, Dr. Bonsall gave an extensive background on methods that have been used and discussed limitations related to the need of using a sex-separation method and late lethality caused by this approach. Next, a density dependent control model for two species of mosquitos was presented, together with ecological consequences of vector control in such a setting (in particular the impact of vector control on biodiversity). In what followed, issues related with cost-effectiveness of different vector control strategies were discussed. A model for dengue virus was proposed and economical outcomes of different control approaches (local eradication, local suppression) was explored. Next, Dr. Bonsall presented a web server developed and maintained by his team that implements these models and strategies, which allows for user-friendly visualization of presented concepts. Also, many issues related to impact of human movement on vector control were discussed. As far as the challenges and further concepts are concerned, biodiversity and human health implications of vector control were pointed out.

THURSDAY, NOVEMBER 7, 2013

Adaptive management and uncertainty
Optimal adaptive management over time and space
Iadine Chades (Ecosystem Sciences, CSIRO Ecosystem Sciences)

Using stochastic dynamic programming techniques, one can optimize decisions over time and space in order to maximize the chance of achieving conservation goals at a minimum cost. Dr. Chades presented uncertain, future dynamics of a system with transition probabilities, and found the best decision when there is model uncertainty using an adaptive management framework. Adaptive management methods tend to suffer from lack of efficiency and realism. To overcome these issues, Dr. Chades and colleagues used partially observable Markov decision processes (POMDP). In some cases, POMDP can be further simplified and approximated with low error. Dr. Chades showed two examples in which she applies these methods: 1) the conservation of Gouldian finches; and 2) management of birds in response to coastal development and future rises in sea level. The POMDP approach does better than the current methods used. The advantages of using POMDP over other current methods include the ability to incorporate non-stationary dynamics and not requiring perfect detection of a species.

Comparing Uncertainties in Natural Resource Management: How to tell what is Most Important

Jacob LaRiviere (University of Tennessee, Knoxville)

Dr. LaRiviere discussed the various forms of uncertainty that can affect management of stochastic renewable natural resources. The forms of uncertainty include stochastic, parametric, mode, and state. While the implications of different types of uncertainty for management have been carefully analyzed individually, it is not clear when each different type of uncertainty is relatively more or less important for the resource manager. In this talk he discussed the challenges of comparing three different sources of uncertainty (state, parametric, and stochastic), and how these may affect the net present value within the same resource management problem. Dr. LaRiviere described and simulated one candidate method for comparing parametric and state uncertainty. He then used an uncertainty metric to show the net present value under these two different forms of uncertainty and the nonlinear effects of uncertainty under different adaptive management strategies.

Avoiding tipping points in the management of ecological systems: a non-parametric Bayesian approach to structural uncertainty

Carl Boettiger (Applied Mathematics and Statistics, University of California, Santa Cruz)

Dr. Boettiger discussed the use of nonparametric approaches that incorporate uncertainty for predicting tipping points. He discussed the challenges in predicting tipping points due to model, parametric, and process uncertainty which pose challenges to robust ecosystem management. With model and parameter uncertainty, predicting tipping points is difficult, because whether the tipping point exists and where in the state-space it might exist is unknown. Dr. Boettiger illustrated how using a Gaussian Process prior gave a more flexible representation of uncertainty. He then discussed how the Gaussian Process prior can be incorporated in a stochastic dynamic programming framework to make robust management predictions under both model and uncertainty and limited data.

FRIDAY, NOVEMBER 7, 2013

Progress and overview

The Friday morning panel included Mary Lou Zeeman, Chris Cosner, Richard Rebarber, Lee Altenberg, Sandy Liebhold and Carrie Manore. The final segment Friday was a general discussion.

Below is a summary of the suggestions and observations made during both sessions.

Suggestions and observations:

- We need more bridges between related disciplines to facilitate communication and research, for example between pure math and applied math, applied math and theoretical ecology, theoretical ecology and conservation, and conservation and policy makers.
- We need more mathematical theory to explore heterogeneity in space and time and the dynamics of transients. We also need to develop a framework for multimodels.
- How robust are objective functions, summary statistics, and scenario rankings to uncertainty and should we define resilience in terms of maintaining transient dynamics or maintaining equilibrium? It was suggested mathematics can address the classification problem.
- We should question disciplinary boundaries that restrain optimal control to a particular space; and instead of managing planet earth, we should manage human power. It was also suggested that the mathematics of bubbles/ autoclytic explosion would be useful.
- How to include uncertainty in control? How to combine game theory with control? What are the mathematical challenges?
- Evolutionary game theory is beginning to be incorporated in adaptive dynamics but is still rudimentary and could be incorporated in ecology-economics questions.
- Considering finite vs infinite time is a question of discounting (typically exponential by hyperbolic may be better. How do we incorporate rewards?
- The usage of robust feedback control to incorporate uncertainty in optimal control was discussed.
- Ecologists and mathematicians need to go beyond eigenvalue analyses in dynamical systems and look at basins of attraction.
- Tenured faculty should change the academic culture by changing tenure promotion to include work that contributes to problem solving and management issues that may not necessarily result in publication.
- It is important to incorporate the socioeconomic component in models to make them more realistic.

Spring Emphasis Semester Workshop 1: Visualizing and Modeling Cellular and Sub-Cellular Phenomena

January 13-17, 2014

Organizers: John Condeelis (Albert Einstein College of Medicine, Yeshiva University), Anna-Katerina Hadjantonakis (Memorial Sloan-Kettering Cancer Center), Paul Kulesa (Stowers Institute for Medical Research), Philip Maini (Mathematical Institute, Oxford University)

Report by: Leopold Matamba Messi, Marc Sturrock, and Lucy Spardy

MONDAY, JANUARY 13, 2014

Motility dynamics during tumor cell dissemination in breast tumors

John Condeelis (Albert Einstein College of Medicine, Yeshiva University)

Dr. Condeelis talk focused on cell dissemination in breast tumors. The central question addressed by his presentation was: *Why do the RhoC/Cofilin/Mena pathways predict metastatic risk in breast cancer?* To approach this question, Dr. Condeelis and his research group have used FRET biosensors and Mutiphoton Intravital Imaging to monitor cancer tumors in vitro and in vivo. The cutting edge imaging tools at their disposal have allowed them to image tumors at single cell resolution providing them with better understanding of breast cancer cells motility. It is now understood that tumor cell movement during streaming and intravasation involves coordination of locomotory protrusions and invasive protrusions; both protrusions involve actin polymerization at the front of each protrusion in response to macrophage produced EGF. Mena activity regulates the sensitivity of the EGFR to EGF thereby increasing invadopodium assembly and streaming migration with macrophages. Cofilin activation is sufficient to determine the site of actin polymerization, protrusion and cell direction. RhoC is part of a signaling complex that regulates the geometry and localization of cofilin activity in both invadopodia and locomotory protrusions determining the shape, size and oscillation of these protrusions during cell migration and invasion. This signaling complex is involved in intravasation and dissemination of tumor cells, thus determining the metastatic phenotype of the tumor.

Modeling the regulation of cell motility in normal and cancer cells
Leah Edelstein-Keshet (Department of Mathematics, University of British Columbia)
Dr. Edelstein-Keshet spoke about an ongoing effort aimed at constructing and analyzing mathematical models for proteins and lipids, their feedbacks and effects on protrusion and contraction of the cell front and rear, as well as shape. She surveyed some of the models produced by her group to date, ranging from single cell wound healing to GTPase spatial patterns. Dr. Keshet illustrated how modeling cell polarity and GTPases has contributed some insights into a more recent endeavor modeling cell motility of mammary carcinoma cells.

Modeling the regulation of Cofilin and Actin based protrusion in invasive tumor cells
Nessy Tania (Department of Mathematics and Statistics, Smith College)
Dr. Tania presented a mathematical model of the regulation of actin filaments growth in mammary carcinoma cells. The model incorporated temporal regulation of cofilin in response to EGF stimulation and the synergistic interaction of cofilin and Arp2/3, as well as diffusible cofilin in active or phosphorylated states. In her model, two compartments linked through diffusion represented the cell: the thin cell edge and the cell interior. The purpose of the model was to address the following questions: *Can cofilin dynamics alone account for the large transient pulse of actin filament barbed ends observed within 1 min of EGF stimulation of carcinoma cells? How does this amplification occur?* Dr. Tania's model demonstrated that a high basal level of active cofilin stored by binding to PIP2, and the highly enriched local milieu of F-actin at the cell edge, are each essential to capture the EGF-induced barbed-end amplification observed experimentally.

Distinct apical and basolateral mechanisms drive PCP-dependent convergent extension of the mouse neural plate
Ann Sutherland (Department of Cell Biology, University of Virginia Health System)
Dr. Sutherland reported on efforts by her research lab to determine what cell behaviors lead to neural convergence and extension in the mouse embryo. Using time-lapse confocal microscopy to

examine the neural plate of live, fluorescently labeled embryos, she found that mouse neural epithelial cells undergo mediolaterally biased cell intercalation and exhibit both apical boundary rearrangement and polarized basolateral protrusive activity, both of which contribute to cell intercalation. Furthermore, Dr. Sutherland identified two proteins associated with planar cell polarity signaling: Ptk7 and Vangl2 Lp. Using knockout mice lines for each of the two proteins, she determined that planar polarization and coordination of these two cell behaviors is essential for neural convergence and extension. Embryos with mutations in Ptk7 fail to polarize cell behaviors within the plane of the tissue, while Vangl2 Lp mutant embryos maintain tissue polarity and basal protrusive activity, but are deficient in apical neighbor exchange. This reveals a novel cooperative cellular mechanism for cell rearrangement during epithelial morphogenesis.

Learning Generative Models of the Dynamics of Cell Shape and Organization Changes
Robert Murphy (Lane Center for Computational Biology, Carnegie-Mellon University)
Given the complexity of biological systems, in silico models of cells that are capable of the functionalities of leaving cells are in great need. Such models require accurate information about the subcellular distributions of proteins, RNAs and other macromolecules in order to be able to capture and simulate their spatiotemporal dynamics. Dr. Murphy presented an open source system he helped design and develop: CellOrganizer (http://CellOrganizer.org). The platform uses machine learning methods on microscope images of cells, organelles, and cellular processes to build generative models of cell organization. CellOrgnaizer is currently capable of building probabilistic generative models of cell, nuclear and organelle shape, organelle position, and microtubule distribution. The resulting models capture heterogeneity within cell populations, can be dependent upon each other, and can be combined to create new higher level models. The parameters of these models can be used as a highly interpretable basis for analyzing perturbations. Generative models of cell organization can be used as a framework for in silico cell simulations to identify mechanisms underlying cell behavior. Dr. Murphy illustrated the usages of CellOrganizer with an analysis of neuronal differentiation and perturbation of plant protoplast organization.

TUESDAY, JANUARY 14, 2014

Imaging approaches in collagen alignment
Patricia Keely (University of Wisconsin)
Dr. Keely presented a range of her lab's work in the area of imaging collagen alignment. She began her talk by stating the need to study cells in tissues without the use of fluorophores – trying to gain as much information as possible out of tissue without perturbing it. She then presented a range of images captured using different methods which, without the use of stains or antibodies, were able to provide insight into collagen alignment. In particular, she presented images of collagen captured using the multiphoton method which makes use of second harmonic generation. She noted that metabolites can be thought of as endogenous fluorophores, i.e., substances that exist inside the cell that can be exploited for the purposes of imaging. She indicated that such fluorophores suffer from only staying in an excitatory state for a short time before relaxing into a more stable state. She then showed that by combining an FLIM image with second harmonic data, one could observe that tumor cells have different lifetimes to other cells. She revealed that a long term goal of her lab is to decipher how tumor reorientation occurs. Her lab discovered that tumors

make use of collagen fibers when seeking out a blood supply. One challenge in this area lies in the many different shapes and structures of collagen. In order to make progress, her group has used 2D models, which are parameterized by the imaging data. The models have yielded the prediction that aligned collagen aids tumor invasion.

Cell decision making during embryonic development
Stefano Di Talia (Duke University)
In Dr. Stefano Di Talia's talk, the process of how cells convert input into outputs was discussed. The model system he used to study this process was embryonic development in Drosophila with a focus on cell cycle control. He began by presenting a video of embryonic development and highlighted the fact that the Mid-Blastula transition (MBT) is key to development. He described the identification of a novel switch-like mechanism controlling the cell cycle pause at the MBT. In contrast to current models in the literature, Dr Di Talia determined that the decision to arrest the cell cycle at the MBT is not controlled by degradation of the maternal mRNA of cdc25, but instead by a switch-like increase in the degradation rate of $Cdc25^{twine}$ protein. He then described the mechanism controlling the entry of cells into mitosis following gastrulation. During Drosophila gastrulation, mitosis is associated with the transcriptional activation of $cdc25^{string}$ which is a phosphatase that activates Cdk1. Dr. Talia revealed that the switch controlling entry into mitosis operates as a short-term integrator, a property that can improve the reliable control of timing of mitosis. He concluded by discussing how this short-term integration may be a more widespread cellular strategy for obtaining reliable and switch-like controls when making decisions.

Functional and Spatial Characterisation of Chromatin States in S. cerevisiae
Karen Lipkow (University of Cambridge)
Dr. Lipkow presented recent work that illuminates the link between cellular architecture and function. She began by reviewing some fundamental topics from molecular biology. In particular she highlighted that the precise combination of DNA and protein at a given location in the nucleus determines how a gene is regulated. She stated that although these protein distributions can be measured experimentally, the resultant datasets were impossible to interpret by eye. She introduced a method that she has developed with her collaborators to analyse chromatin from the model organism S. cerevisiae (baker's yeast). By carefully reducing the complexity of the original data, they were able to identify five distinct chromatin states. These states differed in relevant biological properties, such as enrichment of gene ontologies. Dr. Lipkow then stated that these states formed no detectable pattern in 1D along the chromosomes, but were found to co-localise in 3D. Her work highlighted the great dynamic capability of gene regulation, and emphasised the importance of considering the full spatial dimensionality of a biological system.

Computational Discovery of Events & Phenomena from Microscopy Image Data
Badri Roysam (University of Houston)
In this talk, Dr. Roysam gave an insight into current state of the art microscopy imaging techniques for unraveling cellular events and phenomena. He began by describing the basics of image analysis, particularly with respect to image segmentation, and he stressed the need for reliable automation. Multiplexed fluorescence imaging was introduced as a method that allows associative measurements, and which can relate multiple different cellular structures. Dr. Roysam stated the

difficulty in doing multiplex fluorescence imaging and tracking separately, but revealed that by combining imaging with time-lapse microscopy, multiple phenomena can be imaged in a manner that preserves their relative context. He described progress in the development and integration of multivariate analytics tools into image analysis systems, specifically citing the open source FARSIGHT toolkit, to sense and extract these patterns. Such tools were said to provide a "cornucopia of measurements" for modelers, biologists, and clinicians. He ended his talk by showing the audience an example of high-throughput cell-cell interaction imaging on nano well grids (showing many images and videos). He showed that many interesting behaviors can be discovered using this method. In particular, he presented a study of the ability of immune cells to kill cancer cells. He stated that there are many practical challenges to this method and emphasized how important preprocessing is in order to gain reliable results.

From intravital microscopy to systems view: Tumor cell motility in microenvironment context
Bojana Gligorijevic (Albert Einstein College of Medicine)
Dr. Gligorijevic introduced the events that comprise metastasis to begin her talk. She then reviewed some tumor cell motility biology, stating that previous investigations have dissected the signaling pathways which control locomotion in 2D or invadopodia formation. She motivated her research by asking the question: What is the role of invadopodiea in metastasis, and can they be used to predict metastasis? Through the use of a multiparametric, systems-level analysis, Dr. Gligorijevic showed that it is possible to predict tumor cell motility-related behaviors in vivo. The analysis also reveals the context in which invadopodia or tumor cell locomotion appeared in vivo. She showed a direct link between the number of invadopodia and lung metastasis. Furthermore, she showed that in order to predict invadopodium formation, all the microenvironmental conditions must be studied in unison rather than in isolation. She concluded by speaking briefly about her collaborators' progress on developing a mathematical model of tumor cell motility which makes use of imaging, statistics and molecular biology to produce insights into this complex process.

Revel in the Charm of (Genotypic) "Variety", Relish in the Charm of (Phenotypic) "Fidelity"
Aviv Bergman (Albert Einstein College of Medicine)
Most species maintain abundant genetic variation and experience a range of environmental conditions, yet phenotypic variation is comparatively low. Clearly, development is robust to changes in genotype and environment. It has been claimed that this robustness, which is known as canalization, evolves due to long-term natural selection for optimal phenotypes. Dr. Bergman illustrated this concept by making the audience consider a ball rolling down an uneven landscape, where ultimately, the ball would land in one of few viable niches. In his talk, he considered the causes and consequences of robustness with respect to cancer development. He presented three different examples in his talk: head and neck cancer, cancer metastasis, and the behavioral response to environmental heterogeneity. Dr Bergman described head and neck cancer as a result of breakage of robustness and talked about the limitations of PAM and SAM statistical methods in identifying genes relevant to this kind of cancer. With respect to cancer metastasis, he presented progress in identifying upstream regulators of stable and variable cellular movement genes. In his third example, he spoke about variation in cancer cells behavioral responses based on environmental heterogeneity. He then discussed the limitations of existing experimental methods

and statistical approaches and the need for mathematical modeling approaches to uncover mechanisms responsible for biological phenomena. He concluded by presenting a spatio-temporal phenotypic switch model which included predator-prey-like interactions.

Intravital Microscopy of Cancer Cell Plasticity Through Imaging Windows
Jacco van Rheenen (Hubrecht Institute and University Medical Center Utrecht)
Dr. van Rheenen's talk focused on how tumors metastasize. Through dynamic imaging of the behaviour of single metastasizing cells at subcellular resolution (using two-photon intravital imaging), Dr. Van Rheenen provided insight into metastasis that previous histological techniques have not. Following the recent development of a Mammary Imaging Window (MIW), Dr. Rheenen's group was able to image primary tumors over multiple days in a living mouse. Furthermore, by combing MIW with fluorescent lineage tracing tools, he explained that the lineage of growing mammary tumors could be traced in a dynamic fashion. Such imaging experiments revealed the existence of cancer stem cells which could disappear, and also new ones which could form. He also presented a biophysical model of stem cell competition, which accounted for division, replacement and directional replacement. This model was found to be in excellent agreement with experimental data. He then discussed how tumor cells survive at distant secondary sites and mentioned some experiments his group have conducted in this area. In particular, by imaging abdominal organs like the liver, his group observed that single extravasated tumor cells proliferate and form what he referred to as `pre-micrometastases'. He explained that these cells were later observed to coalesce into micrometastases in which cell migration is minimal but proliferation continues.

WEDNESDAY, JANUARY 15, 2014

Hypoxia and Radiation Therapy
Ruth Muschel (University of Oxford)
Tissue oxygen concentrations are created by a balance between oxygen delivery and oxygen consumption. In contrast to normal healthy tissue, tumors consistently contain regions of extreme hypoxia. In her talk, Dr. Muschel discussed the effects of hypoxia on cancer progression and treatment. In particular, she stated that radiation therapy is compromised severely by the existence of hypoxic regions in tumors. She spoke about her group's efforts to make tumors more sensitive to radiation in order to overcome the nullifying effect of hypoxia on treatment. She showed many strategies her group had tried, for example, through inhibition of the Ras, PI3K and MTOR pathways, hypoxia was decreased but only a minor effect on radiation sensitivity was achieved. In order to better understand the problem, her group developed a partial differential equation model to delineate hypoxia in tumor spheroids. The model was able to predict the hypoxic fraction of cells based on oxygen consumption. This model was also extended to account for vasculature and yielded results consistent with experimental findings. She ended her talk with a series of questions she hoped her mathematical model would be able to address in the future, such as: What would be the optimal temporal sequence for treatment?

Modelling Cancer Cell Migration and Invasion
Erik Sahai (London Research Institute)

Dr. Sahai started his talk by emphasizing the importance of cell migration in the evolution of tumors. As an example, he stated that the local spread of gliomas prevented the surgical removal of such tumors. He stated that there were three inherit problems with studying tumor cell migration, namely, heterogeneity (revealed by microscopy), the switching between migratory behaviors, and variation in the medium through which cells migrate (the matrix geometry). Motivated by the "exquisite control" that mathematical models allow regarding experimental conditions, his group formulated a model of cell motility that accounted for actin-polymerization-based protrusions, actomyosin contractility, variation in actin–plasma membrane linkage (which leads to membrane blebbing), cell–extracellular-matrix adhesion, and variation in extracellular matrix geometries. The model is an agent based single cell model and is parameterized using experimental data. Dr. Sahai showed that the model could produce results in excellent agreement with experimental images (high resolution intravital imaging). The model was used to explore the theoretical requirements for rapid migration in different matrix geometries. His group found that confined matrix geometries cause profound shifts in the relationship of adhesion and contractility to cell velocity. Furthermore, cell–matrix adhesion is dispensable for migration in discontinuous confined environments. He showed that the model could be used to make specific predictions regarding the effect of different combinations of kinase inhibitors and integrin depletion in vivo, and in confined matrices based on in vitro two-dimensional measurements.

Vascular remodeling in the mouse yolk sac

Mary Dickinson (Molecular Physiology & Biophysics, Baylor College of Medicine)

The embryonic heart and vessels form and remodel while functional. Dr. Dickinson talked about her work on uncovering the role and effect of hemodynamic forces on changes in heart and vessel structure. Using time-lapse confocal microscopy and vital fluorescent protein reporters, Dr. Dickinson imaged cultured mouse embryos during vessel remodeling. The data thus recorded revealed that vessel diameter increase occurs via two distinct processes that are dependent upon normal blood flow: vessel fusions and directed endothelial cell migrations. Vessel fusions resulted in a rapid change in vessel diameter and were restricted to regions that experienced the highest blood flow; while directed cell migrations induced by blood flow recruited endothelial cells to larger vessels from smaller capillaries and were located in larger artery segments. Dr. Dickinson's work revealed how sensitive endothelial cells are to changes in blood flow and how such responses drive vascular remodeling.

Decoupling morphogenetic tissue deformations from functional motion in cardiac development

Michael Liebling (Electrical & Computer Engineering, University of California Santa Barbara)

Live microscopy facilitates the observation of rapidly moving samples, such as whole embryos during their development. When the motion is induced by more than a single process, or occurs at multiple temporal and spatial scales, subtler motions and events are often hidden among more prominent, but unrelated, motions patterns. Dr. Liebling discussed in vivo image acquisition, processing, and analysis tools that have been developed at his laboratory to digitally document the morphogenesis and the function of the developing heart. He presented the strategy that he employs to capture and integrate heterogeneous data acquired with multiple microscopy modalities, at

various temporal and spatial scales, and in multiple dimensions. When combined with the digital post-processing strategies afforded by customized algorithms, this heterogeneity of signals allows the observation of cellular division on the surface of the beating heart without the need to ever slow or stop it. This demonstrates the possibility of disentangling complex motion patterns through customized imaging and digital post-processing strategies.

In vivo study of the intact mouse by non-invasive tomographic imaging
Sean Smart (Department of Oncology, Oxford University)
Imaging is used to measure the spatial distribution of certain phenomena, and depending on the phenomenon, some imaging modalities are more effective than others. Dr. Smart illustrated how this plays out with various in-vivo studies of the intact mouse using multiple imaging modalities: CT, SPECT, MRI, and PET. CT imaging was used to generate images of the skeleton; thus allowing to measure bone density, inter-bone angles and joint movement. SPECT imaging was used to study DNA damage in the intact mouse, and to assist in the development of better molecular tracers. Dr. Smart's team used high quality MRI to screen liver and prostate tumors in living mice, and fast imaging to study tumor blood flow. They combined PET and MRI tomograms to study cardiac structure and function, and estimate the heart and lung blood volume. Using imaging in basic science research is a highly collaborative endeavor between engineers, chemists and biochemists, biologists and medical doctors, computer scientists, mathematicians, and statisticians.

THURSDAY, JANUARY 16, 2014

Cellular mechanisms underlying the fomation of the primitive steak formation in the chick embyro
Kees (Cornelis) Weijer (University of Dundee)
Dr. Weijer discussed ongoing work on the mechanisms controlling the formation of the primitive streak in amniote chick embryos. During primitive streak formation, mesoderm cells are transported into the central midline, due to counter rotating cell flows in the epiblast. Simultaneous with the formation of the streak, the hypoblast develops and extends in the anterior direction. Hypotheses for the mechanism underlying streak formation include chemotaxis, local cell-cell intercalation, and oriented division, but detailed quantitative data supporting any of these hypotheses is currently lacking. Dr. Weijer described recent findings made using new tools – namely, a dedicated light sheet microscope that can investigate the cellular dynamics in greater detail. His results support a novel mechanism for streak formation based on localized shape changes resulting in ingression as well as intercalation of mesendoderm cells.

Modelling Collective Cell Motion in Biology
Philip Maini (Centre for Mathematical Biology, University of Oxford)
Dr. Maini gave an overview of different modeling approaches to collective cell motion, including cranial neural crest cell invasion, epithelial sheet dynamics, and acid-mediated invasion. In each case, Dr. Maini described how the models informed various biological issues. The vertex-based model in the early mouse embryo proposed a role for rosette formation. The individual-based model for neural crest cell invasion proposed two cell types necessary for succesful invasion. For acid-mediated tumor invasion, Dr. Maini showed how the model suggested therapeutic strategies for tumor control.

Modeling and Imaging of Cell Aggregation
Mark Alber (University of Notre Dame)
Dr. Alber discussed the ability of animals to self-organize in patterns, using the bacterium M. xanthus and P. aeruginosa as examples. He described the mechanism underlying the collective movement of the soil bacteria M. xanthus, using model simulations and experimental movies captured through high-resolution time-lapse microscopy. He also showed how P. aeruginosa (a main infection in hospitals) propagates as high density waves, and suggested a mechanism of wave propagation using results from biologically-justified cell-based multiscale model simulations. This mechanism depends upon competition between the changing viscosity of the bacterial liquid suspension and the liquid film boundary expansion caused by Marangoni forces. Dr. Alber confirmed the model predictions of wave speed and swarm expansion rate as well as cell alignment in tendrils experimentally.

Image analysis and pathology: the raw and the cooked
Richard Levenson (University of California Davis)
Dr. Levenson showed many examples of correctly classified images from the machine-learning software he uses which differentiates based on texture similarities and neural nets. He asked three questions: What is the semantic overlap of texture and structure? Where (at what scale?) does information reside? and Should computers emulate the role of pathologists? He also discussed recent work using multiplexed ion beam imaging that allows pathologists to look at a large number of proteins simultaneously in cells with microscopic resolution, and the computational challenges that poses.

Mathematical modeling and biomedical imaging of anti-cancer drug penetration
Katarzyna Rejniak (Moffitt Cancer Research Institute)
Dr. Rejniak introduced a mathematical model used to systematically explore the role of tumor tissue architecture and stromal composition on the extent of drug and biomarker molecule penetration into the tissue. She presented the current state of the computational model integrated with experimental data and calibrated to pancreatic tumor xenografts. Her aim is to provide an analytical tool in designing drug properties and drug administration schedules that will optimize drug penetration into the tumor tissue and enhance their therapeutic efficacy. She highlighted a number of challenges, including the fact that quantitative measurements can be on different scales (in vivo or in vitro), the lack of temporal data, and the difficulty in comparing images from the model with image-based experimental data.

Mathematical modeling of neural tube patterning
Karen Page (University College London)
A major challenge for developmental biology is to understand the mechanisms underlying pattern formation. In her talk, Dr. Page addressed this challenge by discussing how prospective neurons make the decision about what type of neuron they will become. Conventional views say that morphogens induce distinct responses in a concentration-dependent manner, but signal duration has also been implicated in determining cellular responses. Dr. Page introduced the morphogen Sonic Hedgehog (Shh), and showed how the level and duration of Shh signaling controlled

patterning in the vertebrate neural tube. She then described the transcriptional regulatory circuit that links Shh signaling to transcription factors, with equations that described the levels of the transcription factors within a cell. She showed that the design of the circuit unifies the temporal and graded response to Shh signaling. It also renders cells insensitive to transient increases in Shh signaling and confers hysteresis - memory of the signal. Dr. Page verified these results experimentally, and discussed alternative behaviors of the gene regulatory network.

FRIDAY, JANUARY 17, 2014

NAD+ biosynthesis ameliorates muscular dystrophy in zebrafish
Clarissa Henry (University of Maine)
Dr. Henry discussed an in vivo model for musculoskeletal development and homeostasis in the zebrafish. To illuminate the molecular mechanisms underlying muscle morphogenesis, she aimed to first understand the cellular mechanisms underlying muscle morphogenesis. Dr. Henry described how cell adhesion guides the phases of muscle cell elongation, and revealed that the fundamental question is to understand how data is integrated and processed by cells to generate those morphogenetic outputs. She concluded her talk by showing that NAD+ supplementation improves organization in a disrupted basement membrane (a hallmark of dystrophies), and suggested that the bony fish muscle is a great model to understanding cell biology of morphogenesis, with applications to disease and injury.

The influence of spatial variation in chromatin density on the time to find DNA binding sites
Samuel Isaacson (Boston University)
Dr. Isaacson described his recent work investigating how volume exclusion due to the spatially varying density of DNA in the nucleus influences the time required for proteins to find DNA binding sites. To approximate the drift-diffusion process, a protein undergoes as it searches for a binding site, he derived a lattice master-equation model. Several different types of high-resolution imaging of the interior of mammalian cell nuclei allowed him to construct detailed three-dimensional simulations of the protein's search process. Finally, using asymptotic expansions, Dr. Isaacson developed a mathematical theory to explain the observed simulation results.

Tissue patterning with RNA oscillations: single cell resolution imaging of segmentation clock dynamics
Sharon Amacher (The Ohio State University)
Dr. Amacher discussed a basic question for developmental biologists: how are cells able to tell time -- how do they know at Day 1 where they will be at Day 11? She introduced a prevalent model used to describe the process of segmentation in zebrafish, called the clock and wavefront model. This model assumes segmentation is controlled by an internal oscillator. The molecular mechanism through which oscillations occur is controlled by an auto-regulatory negative feedback loop. Dr. Amacher discussed the molecular trigger for this clock and what components were required for its performance. Her results showed that the clock could be visualized at single cell resolution, and highlight the importance of Notch signaling for maintaining synchrony.

Is 3 the magic number? Exploring the EGF/CSF-1 paracrine signaling between macrophages and tumor cells

Hildur Knutsdottir (University of British Columbia)

Experiments have demonstrated that macrophages are directly involved in the invasion of breast tumor cells into surrounding tissues and blood vessels. The macrophages interact with tumor cells via an EGF/CSF-1 paracrine signaling loop. Dr. Knutsdottir developed a 3D individual cell based computational model to study the interaction between macrophages and breast tumor cells and to understand the observed streaming motility pattern. Her model incorporates the paracrine signaling loop between tumor cells and macrophages, with cells simulated as freely moving discrete deformable ellipsoids. This simplified model is sufficient to reproduce results from both in vitro and in vivo experiments, and suggests that the removal of the signaling molecules is essential to produce the noted ratio of 3 invasive tumor cells per 1 invasive macrophage. A parametric sensitivity analysis revealed that the invasive ratio between tumor cells and macrophages is robust to changes in most model parameters, except to changes in the degradation and secretion rates of EGF and CSF-1.

Spring Emphasis Semester Workshop 2: Morphogenesis, Regeneration, the Analysis of Shape

February 10-14, 2014

Organizers: Thomas Lecuit (Developmental Biology Institute of Marseille), L. Mahadevan (Harvard University), and Ross Whitaker (University of Utah)

Reported by: Jae Kyoung Kim, Wenrui Hao, Jay Newby

MONDAY, FEBRUARY 10, 2014

Describing Phonotypical Differences with Extracted Shapes

Raghu Machiraju (Ohio State University)

Genotype space is usually abundant and heritable and phenotype space is which we have interest in. Dr. Machiraju discussed about an inverse problem between genotype space and phenotype space. In particular, he presented three examples of visualizing phenotypical changes arising from genotypical changes in a variety of biological contexts from cancer and developmental biology. First, he explored spatiotemporal patterns of gene expression in a developing mouse brain over the six pre-adulthood stages. For this, the gene expression data are analyzed by using Hierarchial Orientation Structure Tree. This allows the encodings of time, space, and functions of gene expression in structure formation. Second, he showed how changes in shape of the tissue interfaces can be used to explain genotypical changes. The tissue interface of WT and Rb-/- are analyzed with the level set method and evolution distance metric, which supports the Reone's hypothesis. Finally, he described how to detect the group-wise changes in the shape of nuclei of salient cells in the microenvironment as noted in knockout mouse and wound-impairment studies. By using multi-spectral confocal method, nuclei phenotypes of WT, p53-/- and PTEN-/- cells are analyzed, which shows the large difference in the outside layer of nuclei in mutant cells.

Extending the concept of shape beyond structural morphology with chemical imaging

Rohit Bhargava (UIUC)
Detecting the microscopic structural features is critical to the diagnosis of solid cancers. Dr. Bhargava presented a novel chemical imaging technique, which provides a way to detect the microscopic structure. His method uses chemical imaging rather than stains, computation than manual detection, and smart microscopy, which provide chemistry as well as structure information. For this, spectroscopic imaging is used to detect the different cell types with computation. Furthermore, FT-IR imaging technology provides combined image of spectroscopy. This new method improves the efficiency in the examining the large samples, reduces the error via pro-diagnostic quality control. Furthermore, this new method provides a rapid breast pathology, which allows a simple and rapid evaluation of tissues. Currently, he tries to apply the method to detect a single molecule in multiple cells with nano technology.

Unpacking neuronal form and neighborhoods from connectomes
Robert Marc (University of Utah)
Dr. Marc discussed the connectomics that explores the connectivity of neurons in the brain. Mapping the neural networks in the brain requires the comprehensive list of parts, nanometer scale connection detection and millimeter scale network tracing. For this, he used TEM compliant molecular markers and an automated TEM imaging method, which allows the detection of network among different neuron types with 2nM scale in the retina. However, the complexity of the neuronal network makes it challenging to understand the structure. Dr. Marc presented various approaches to unpack the complexity of network in the retina. Through systemic scale unpacking, the inner plexiform layer is refactored. Through cell scale unpacking, 8 connected coverings in AII cells are found. Finally, network scale unpacking identifies the Rod-cone decision network.

Maternal alcohol exposure: impact on genetic control of craniofacial phenotype
Murat Maga (Seattle Children's Hospital)
Dr. Maga discussed a method to document and understand how and when prenatal exposure to alcohol begins to impact the craniofacial form, which is known as Fetal Alcohol Spectrum Disorders (FASD). For this, he used animal models with small animal tomographic tools (both optical projection and micro computed tomography). He found that chronic maternal exposure to alcohol results in different brain size, philtrum, distance between olfactory and bulbs, skull length and snout width. Furthermore, the effect of alcohol becomes stronger in the mid-fetal stage than later development stages. The challenging part of studying FASD with this approach is the tedious manual segmentation of the brain and the effect of image modality on continuity of data collection, which will be an important direction for future work.

Inner ear size and shape is regulated by pressure, transport, and tissue mechanics
Kishore Rao Mosaliganti (Harvard University)
How do animals develop similar organ sizes and shapes despite large fluctuations in initial growth conditions? How is size and shape control achieved across molecular-cellular-tissue scales? Dr. Mosaliganti answered these questions in the context of early ear development that exhibits a highly stereotyped pattern of assembly and growth. Using in toto imaging technologies in the zebrafish embryo, he and his team reconstructed morphogenetic patterns of cellular movements, cell number and shape changes, and tissue topology changes. They showed that otic vesicle growth and

regeneration is characterized by endolymph pressure and tissue stretching forces that provide feedback to circuits responsible for generating endolymph fluid. To systematically investigate how otic vesicle growth is controlled, they developed a minimal mathematical model linking tissue geometry and mechanics to tissue stretching forces, thus illuminating how size control to stage-specific volumes is accomplished. Because ear development shares many features with other developmental (eye, heart, kidney) and disease processes (tissue tumor formation), their results and mathematical model will inform understanding of the morphogenesis of other organs.

Cell shape determination in single-cell motility
Julie Theriot (Stanford)
Dr. Theriot discussed the connection between cell shape and cell motility in a single cell level. Specifically, her research is aimed at answering the following two questions: 1) How are shape and movement coupled via cytoskeletal elements? and 2) Can we predict movement behavior from shape or vice versa? For this, she examined keratocytes in fish. One interesting observation is that keratocytes with the same genotype can have varying shapes. However, there are no obvious morphological landmarks, so various approaches have been tried. She determined that PCA of outlines of cells performs best for reconstruction and for separation of experimental group. By applying this method, she found four significant principal and orthogonal modes of keratocyte shape: size, aspect ratio, wing angle, and left-right asymmetry. Furthermore, this characterization of cell shapes leads to a general force-balance model for cell shape determination, such as 1) the effect of VASP and actin density on aspect ratio, 2) the relationship between adhesion promoter and wing angle, 3) and the effect of shape of turning on left-right asymmetry. Finally, she applied this approach to more complex cell types and cell behaviors in the presence of environmental cues. For this, she used neurotrophils, whose shape also can be analyzed with four orthogonal modes: elongation, asymmetry, and leading edge width and uropod thickness.

A distance on curves using orthogonal transformation
Jaap Eldering (Imperial College London)
Dr. Eldering presented how to measure the dissimilarity and distance between 1D curves, such as the boundary of 2D objects, and trajectories in systems. His research goal is to find a norm or distance on the space of curve shape that can be calculated efficiently and that can also provide a good measure of dissimilarity. To develop this metric, he used jets (Taylor polynomials), which give local description of curves, to compare curves. Then, he applied the orthogonal group elements on frame coordinates at each curve so that two curves have the same local coordinates. Then, he used the L2 norm to measure the distance between two curves locally. Finally, this local distance is integrated over the curve with non-constant orthogonal group elements, adding a penalty for variation. This defines a distance on curves modulo rigid transformation. Currently this method is not free of the parameterization of the curves, but this issue should be resolved in the future.

TUESDAY, FEBRUARY 11, 2014

Airway tree-shape modeling through large-scale tree-space statistics
Aasa Feragen (University of Copenhagen)

Dr. Feragen presented the airway tree model to represent transportation systems that distribute blood, water or air. She introduced the model assumptions, the tree representation and tree-space, and some useful properties of airways. Then she outlined the algorithm to solve the geodesic airway model numerically. She also talked about applications to an anatomical labeling of airway trees, and to large-scale statistics on the effect of Chronic Obstructive Pulmonary Disease on airway trees. By investigating reproducibility on a large longitudinal dataset, she found that segmentation problems seem to affect the model.

Finally she pointed out a difficulty to deal with: What is a "line"? How do you parameterize a "line"? How do you optimize over a family of "lines"? She has also done work to generalize this model to the lungs and other parts of the body.

Computational Neuroanatomy Mapping brain structure for differential discrimination in Dementia

Mirza Faisel Beg (Simon Fraser University)

Dr. Beg briefly gave some background on neuroimaging in dementia, and pointed out that Alzheimer's dementia is a progressive pathology. Then he introduced discrimination between AD, FTD and controls using the volumes of hippocampus and ventricles. He also talked about multi-structure whole brain registration and residual variance in image intensity after registration. He then presented whole brain registration for neuroanatomy morphometry: VBM and TBM. He followed with some results on dementia specific pattern of neurodegeneration with unified statistical parametric maps, and some visualization of whole brain SPMs, which reveal dementia specific pattern. Finally, he summarized the network, showed the choice of classifier, compared three configurations, and drew the conclusion that simple volumes have good classification for this particular problem

Diffeomorphometry of f-shapes

Alain Trouve (Ecole Normale Superieure, Cachan, France)

Shape spaces have emerged as a natural mathematical setting to think about shapes as a structured space. In that setting, group actions of diffeomorphisms provide nice vehicles to build a full processing framework called here diffeomorphometry. In this talk, Dr. Trouve presented a recently developed framework embedding the situation of geometrical shapes carrying functional information called here f-shapes. He finished by showing some applications in computational anatomy, scene interpretation, and entropy image reduction.

Comparative analyses of mandibular growth using Procrustes-based geometric methods

Miriam Zelditch (University of Michigan)

Evolutionary biologists study ontogeny both to dissect the modifications of development that generate morphological diversity and to obtain a comprehensive view of phenotypes. The central concept in ontogenetic studies of form is the ontogenetic trajectory. But in the first published paper, there is more information about the important parameter sigma. In this talk, she explored some important questions about ontogenetic trajectories, and studied different phases. She then applied to mandibular development, and showed that the ontogenetics of mandibular development is too complex to represent by a single straight line.

Dr. Zelditch also showed some other applications of ontogenetic series: Mus musculus and Otospermophilus beecheyi. Finally, she used Procrustes-based geometric methods to determine how developing parts of a functional whole are coordinated, to analyze the relationship between developing form and function, and to determine why some groups are more evolvable than others.

Metric-Based Registration, Comparison, and Modeling of Shapes of Objects
Anuj Srivastava (Florida State University)
Dr. Srivastava talked about some metric-based shape analysis scenarios, which includes Landmark-based shape analysis, shape analysis of curves, parameterized surfaces image-registration using metric considerations, and analysis of trajectories on Riemannian manifolds. After reviewing some general shape analysis in a general framework, he also showed that re-parameterization controls registration and preserves shape. This leads to a natural question about the choice of metric. Then he talked about several approaches to answer the proposed question: 1) an elastic Riemannian metric; 2) shape spaces of open curves; 3) "colored curves"; 4) covariance and principal modes. Then he gave affine-invariant shape summaries. Finally, he presented metric-based shape analysis versus model-based shape analysis, and some applications including square-root velocity functions for curves and square-root normal fields for surfaces.

Transport-based morphometry for modeling and discrimination of image data
Gustavo Rohde (Carnegie Mellon University)
Numerous applications in science and technology depend on quantitative information extraction from data whose dimension is large compared to the number of samples available. In this talk, Dr. Rohde described a novel image analysis framework that, in contrast to deformation-based morphometry, can be used for modeling and discrimination of shape and intensity (e.g. texture) information for a wide variety of imaging problems. The approach consists of an analysis as well as a synthesis operation (i.e. a signal transform) which not only provides a linear embedding isometric to a linearized version of the well known optimal transport metric, but is also invertible. Computational methods for implementing the framework were described, and the approach was demonstrated in modeling and discrimination in image databases of cells and faces. He showed that the method can not only achieve high discrimination accuracies, but also allow for straightforward visualization and interpretation of the information present in such databases. He also described efforts in modeling cellular phenomena from microscopy images using deformation and transport-based methods. The models described have been implemented or are being implemented in their open source system, CellOrganizer, which can learn generative models of cell organization and synthesize new images drawn from those models.

WEDNESDAY, FEBRUARY 12, 2014

Growth and form of the vertebrate gut and the primate brain
L. Mahadevan (Harvard School of Engineering and Applied Sciences)
Dr. Mahadevan began by referencing the 100th anniversary of D'Arcy Thompson's landmark work "On Growth and Form", and then introduced his topic: gut patterning, brain gyrification and wing shape. He gave some background of "how guts loop" by using a chick embryo, and proposed a

related packing problem. In order to solve this packing problem, he presented his physical model with two variables: mesentery and cut. This model is based both on the topology and on results of biological experiments, and can capture the mechanical properties such as elasticity of the tube. He then talked about the computation of the model, which is divided into several triangular domains and based on finite element analysis. He also showed some comparisons between numerical simulation and experimental data. Meanwhile, he proposed another question "what happens inside the gut"?

Statistical Shape Analysis in Computational Anatomy
Laurent Younes (Johns Hopkins University)
Dr. Younes described a shape analysis pipeline in medical imaging that starts from a dataset containing segmented regions of interest. He began his talk with a brief introduction of shape spaces, and two examples: Kendall Shape spaces and deformable templates. Then he introduced a tangent space representation in Exponential Charts, which provide a natural way to build linear representations. He also gave a numerical simulation and showed how to compute a shape that is central to the dataset. The approach is based on the flow associated with an ODE mapping. Then he talked about the geodesics for diffeomorphisms, which are used to compute the shape spaces. The numerical algorithm is used to control shape evolution using velocity vectors through minimizing the metric via "Riemannian submersion".

Statistical analysis of shapes of 3D objects
Sebastian Kurtek (Ohio State University)
Dr. Kurtek talked about the shape analysis of 3D objects, which is described by their boundaries. The main goal is to measure distance between shapes. The second goal is to determine invariants to shape preserving transformations. This study is based on Riemannian statistics and parameterized surfaces. Before presenting his method, he gave some background on square root normal fields (SRNFs), which is a special representation of surfaces. This is also a related elastic Riemannian metric. His method includes three parts: 1) interpretation of shape deformations; 2) re-parameterizations of surfaces; 3) elastic L2 metric. This new framework brings a new tool to register, compare, and summarize variability. Then he gave several examples arising from medical imaging and graphics to demonstrate the efficiency of the new approach. Finally he introduced some properties of shape, such as average shapes and covariance, which are useful for random sampling.

Morphogenesis of Tetrapod Digits
Kathryn Kavanagh (University of Massachusetts Dartmouth)
Hands are perfect mirror images even though they develop in complete isolation. However, variations exist among individuals, and there are interesting questions about robustness and variation. What are the construction rules for digits? Digits originally developed from fins. The earliest organisms with fins had 8 digits, and no fossils have been found without segmented digits. Also, joint positions are biomechanically important, and this influences the evolution of digit morphology. For example, perchers, walkers, and runners all have different digit morphology that ostensibly corresponds to the biomechanical requirements of locomotion. However, decades of advances in genetic regulatory studies of the limb have been unable to accurately model regulation

of digit segmentation using developmental genetic signaling interactions alone. In this context, Dr. Kavanagh discussed alternative models of morphogenesis of segmented structures, such as the digits, in which physical tension between cells, evolutionary origins, and high-level network dynamics are considered.

Mean and Variance of Metric Trees
Megan Owen (University of Waterloo)
Phylogenetic trees describe species that evolve. Different biologists may get different trees based on different genetic data. A common viewpoint is that the shape of a tree is important to the data but cannot be represented in Euclidean space. Starting with labeled tree data, each tree edge induces a split, which is a partition of the set of leaves. The tree is first represented as a vector in a finite dimensional tree space, where the coordinates represent the splits. In this framework, the data starts looking more Euclidean. However not all sets form a split, therefore the data cannot be represented using Euclidean geometry. The space is hyperbolic, and there is a unique geodesic path (shortest path) between two trees. It is then possible to define a mean and variance of the distribution of trees, which can be computed in polynomial time.

THURSDAY, FEBRUARY 13, 2014

3D Actin Network Centerline Extraction with Multiple Active Contours
Xiaolei (Sharon) Huang (Lehigh University)
Actin filaments and microtubules form the skeletal structure of the cell. Sometimes filaments are bundled to provide increased strength and structure. Imaging cytoskeletal filaments is very challenging because of their 3D structure. An automated computer algorithm can extract these objects from imaging data. The method uses "Stretching Open Active Contours" (SOACs). The centerline of a filament can be tracked though the imaging data of curvilinear networks.

Geometric algorithms for shapes and trajectories
Carola Wenk, (Tulane University)
In this talk, Dr. Wenk gave an introduction to geometric algorithms for comparing and matching discrete geometric shapes such as point sets, polygonal curves, and graphs. She presented measures for shapes, approaches for matching shapes under transformations, and algorithms for reconciling sets of shapes by constructing simpler representative shapes. She also considered theoretical results as well as real-world applications including biomedical imaging and GPS trajectory analysis.

The Role of Imaging in Phenotypic Screening
Jens Rittscher (IBME, University of Oxford)
To set the stage, Dr. Rittscher introduced the phenotypic screening and the relevance of this approach to drug discovery. The talk highlighted a number of image analysis techniques that play an increasingly important role in phenotypic screening. In particular, he reviewed algorithms for cell tracking and cell cycle estimation as well as image analysis based approaches for tissue mapping. Apart from discussing the image analysis algorithms the presentation also outlined what work will be necessary to integrated the high-content information in the overall workflow. Ongoing work at the newly established Target Discovery Institute (TDI) at the University of

Oxford was also presented, and the overall goal and the research objectives of the different groups at TDI were discussed.

Domain-specific shape correspondence for brains, out-flow tracts, and bat pinnae and noseleaves

Cindy Grimm (Oregon State University)

Shape and function are intricately related in biology. Dr. Grimm presented three biological case studies where the goal is to quantify shape change in order to analyze how shape informs function. Biologists have specific questions they are interested in answering, and have domain knowledge that should be incorporated into the shape correspondence algorithm. She showed how to incorporate these constraints into the shape matching algorithms in order to provide her collaborators with biologically-meaningful shape correspondences.

- Case study 1: Using strain to track ferret brain development.
- Case study 2: Using geodesic distances and an approximate medial axis to track an in-vivo beating chicken hearts at an early stage of development (peristaltic motion).
- Case study 3: Shape space based on natural neighbor coordinates for bat pinnae and noseleaves.

FRIDAY, FEBRUARY 14, 2014

Discussion

Ross Whitaker (University of Utah)

In the discussion sessions, participants shared various important questions for future research directions. What are the practical aspects of real data, and what kinds of data sets can we expect to see in both biomedical and biological point of view? What kinds of software/tools are people using, and what would it take to get a new method adopted? Given the question "What enables/prevents effective collaboration between these communities?" various tips were shared by participants: 1) face meeting with collaborators, 2) interdisciplinary institute, such as MBI, 3) finding a common interesting problem via persistent communication, and 4) sharing the software via webpage, so that biologists can see the usefulness.

Participants also extensively discussed "how do we know when registration, metric, and method are good?" For instance, people discussed the case when the results are different depending on model and metric choice. One answer was that both results would be meaningful because different model or metric shows the different aspects of data. The risk about this approach was raised, pointing out the potential bias in the choice of metric or model.

Finally, participants discussed what aspects of the problem current approaches and methods are missing. Several important points that are needed for future research were made: 1) flexible ways for data integration, 2) unbiased metrics and models, 3) ITK projects that integrate various tools, and 4) standard protocols for data analysis.

Spring Emphasis Semester Workshop 3: Integrating Modalities and Scales In Life Science Imaging

March 17-21, 2014

Organizers: Monica Hurdal (Florida State University), Michael Liebling (University of California Santa Barbara), Rob Macleod (University of Utah), Kristin Swanson (Northwestern University)

Report by: Josh Chang, Leopold Matamba Messi, Lucy Spardy

MONDAY, MARCH 17, 2014

Mechanics matters: macro, micro, nano

Peter Kohl (Imperial College London)

This talk provided an overview of topics that are sometimes overlooked in studies of the heart. Scientists tend to simplify the heart into an electrically-controlled chemically-driven pump while paying less attention to the mechanical environment in which the heart lies. This mechanical environment has large influence over many important aspects of the heart that are studied, including electrophysiology, contraction, calcium handling, and response to drugs. For this reason it becomes important to understand the three-dimensional organization of the tissue and its effect on phenomena at many levels spanning the nano-scale to the macroscopic.

Dr. Kohl's group has focused on how the three-dimensional organization of tissues, cells, and subcellular structures influences cardiac mechano-sensitivity. These studies were guided by information obtained from imaging data, where human case-specific structure information can be inferred. From this data, and from computational modeling involving the intricate and salient aspects of heart conduction, the relevant features of the organization of the tissue that affect conduction can be determined. These studies highlighted the potential of 3D structure-function mapping as a paradigm for exploring basic research that is clinically relevant.

Anatomically accurate multiscale-multiphysics models of total cardiac function

Gernot Plank (Dalhousie University)

Despite the overwhelming wealth of data available today, gaining mechanistic insight into cardiac function remains to be a challenging endeavor. Complex interactions underlie the very nature of cardiac function, on multiple scales and across electrical, mechanical, and fluidic systems. While computer simulations are a powerful adjunct to experimental studies, there are limitations to the current modeling methodology, which forces research to resort to overly simplified modeling assumptions. Dr. Plank highlighted recent advances in modeling organ scale cardiac anatomy and electro-mechano-fluidic function at high spatial resolution. His methods aim to enable computational studies where model complexity is chosen as a function of the question being addressed, and not based on feasibility constraints. He highlighted the importance of advanced numerical methods to reduce execution times and facilitate quick simulation-analysis cycles. He also showed examples, including multiscale arrhythmogenic effects due to mitochondrial dysfunction and calcium handling, as well as clinical modeling studies which aim at optimization and outcome prediction due to interventions such as aortic valve replacement and repair of aortic coarctations.

Deriving Macroscopic Parameters for Computational Modeling of Cardiac Tissues from High-Resolution Three-Dimensional Confocal Microscopy

Frank Sachse (University of Utah)

Computational models play an important role in studies of cardiac tissue physiology and pathophysiology. Various types of models have been developed based on histological and electrophysiological studies, including monodomain, bidomain and multidomain models of cardiac conduction. Dr. Sachse introduced multidomain modeling of cardiac conduction, and described the general approach and current issues of confocal microscopy. He described the methods he has developed for deriving model parameters from three-dimensional reconstructions of cardiac tissue at sub-micrometer resolution. The reconstructions are created using image data from fluorescent labeling and scanning confocal microscopy. His work provides important input for parameterization of models of cardiac tissues, in particular, models for investigations of tissue remodeling in disease and restoration after therapy.

Biofuel cell polarization estimation: Inversion of electrochemical impedance spectroscopic measurements Importance of model formulation

Rosemary Renaut (Department of Mathematics, Arizona State University)

Dr. Renaut spoke about the inverse problem associated with electrochemical impedance spectroscopy. The goal of the problem is to infer the equivalent circuit model for a biofuel cell polarization experiment, the underlying resistance and number of processes, and the chemical environment that minimizes Anode-Respiring-Bacteria potential loss from electrochemical impedance spectroscopy measurements. The impedance measurements are a function of angular frequency, which is expressed as a Fredholm integral with unknown distribution of relaxation times (DRT). Dr. Renaut introduced two models: the simple resistance-capacitance circuit model with a simple analytical formula for the impedance function (RQ model), and the resistance-capacitance circuit with lognormal distribution of relaxation times model (LN model). She presented experiments comparing the two models on simulated data and demonstrated that the model with the smallest residual errors does not give the best fit. However, a change of variable in the impedance function improves the quality of fit. Still, to obtain feasible solutions, the addition of a non-negativity constraint is required. The computed fit which uses non-negatively constrained least squares with higher order smoothing produces higher quality solutions than those without non-negativity constraint. Dr. Renaut indicated that the techniques used on this project could be extended to the broader framework of solving Fredholm integral equations for other applications. This work was done in collaboration with a team of undergraduate students.

In vivo imaging of the developing mouse brain: From morphology to molecules

Daniel Turnbull (Skirball Institute of Biomolecular Medicine, NYU School of Medicine)

Dr. Turnbull's lab has developed a combination of ultrasound and magnetic resonance micro-imaging approaches with sufficient resolution and sensitivity to provide non-invasive structural, functional and molecular data on developmental and disease processes in normal and genetically engineered mice. In this talk, Dr. Turnbull presented several examples of the uses of these techniques for in utero and postnatal imaging and analysis of the developing brain and cerebral vasculature.

High frequency ultrasound is used to increase resolution of the images and capture 3D images in a very short time. They used this modality to do a volumetric analysis of mouse fetal development and understand how the brain, the neural tubes, and limbs develop during gestation. Ultrasound is also used to record cardiac dynamics in vivo. High frequency MRI is used in combination with registration methods to generate 3D images of the mouse embryo in-vivo. The images are then used to extract vascular maps and brain ventricular structures of mouse embryos, which in turn are used to understand how both the vasculature and ventricular structures develop during gestation.

Recently, Dr. Turnbull has focused on developing new modalities that combine ultrasound and MRI for molecular imaging. His lab has developed a biomarker – dubbed biotag -- that uses biotinylation of vascular endothelial cells. The biotag marker was used as a contrast enhancer in transgenic biotin expressing mice to generate improved visual maps of the vasculature using MRI imaging. Manganese-Enhanced MRI (MEMRI) is being used in longitudinal imaging to study the development of the brain during gestation with a special focus on the development of the cerebellum, and on cerebellar foliation. Dr. Turnbull also presented various uses of MEMRI to detect activity in the developing brain as well as to detect neural activity.

TUESDAY, MARCH 18, 2014

Toward Making the Invisible and Complicated Understandable: Microscopy Across Scales and Modalities

Mark Ellisman (University of California San Diego)

Dr. Ellisman began with one of the goals of cell biology: to understand how the interplay of structural, chemical and electrical signals in and between cells gives rise to tissue properties, especially for complex tissues like nervous systems. New technologies are hastening progress towards this goal, as biologists make use of an increasingly powerful arsenal of tools and technologies for obtaining data from the level of molecules to whole organs. They also adapt and assemble data at all scales of resolution and across disciplines into computerized databases. Dr. Ellisman highlighted projects in which development and application of new contrasting methods and imaging tools have facilitated the observation of otherwise hidden relationships between cellular, subcellular and molecular constituents of cells, including those of nervous systems. He described new chemistries for carrying out correlated light and electron microscopy, as well as recent advances in large-scale high-resolution 3D reconstruction with LM, TEM and SEM based methods. Finally, he showed examples of next generation cell-centric image libraries and web-based multiscale information exploration environments for sharing and exploring this data.

Predictive Patient-Specific Mathematical Neuro-Oncology: A Paradigm Shift in Glioma Treatment

Kristin Swanson (Northwestern University)

Gliomas are highly invasive primary brain tumors, but their diagnosis and treatment relies on tissue imaging, which limits our knowledge of tumor complexity. Dr. Swanson introduced a clinical imaging scale model for glioma proliferation and invasion, which could be calibrated to each patient's spatial patterning. She showed how predictions from the model can aid or inform clinical

decision making. The goal of her work is to address some primary clinical challenges, including: who will respond to therapy, or standard care? How much will each patient respond? How long will they live? How can we optimize treatment for each patient?

Advances in multiphoton microscopy for high-content in vivo imaging
Willy Supatto (Ecole Polytechnique)
Light-sheet microscopy has gained widespread recognition due to its distinct advantages for imaging live organisms with high acquisition speed, large field-of-view, and low phototoxicity. However, its imaging depth remains a limitation. On the other hand, multiphoton microscopy achieves high imaging depth into scattering tissues and permits multimodal detection, including the combination of fluorescence and harmonic generation as sources of signal. However, its acquisition speed is limited, and it remains challenging to obtain efficient multicolor excitation. In his talk, Dr. Supatto highlighted the recent advances in multiphoton microscopy to improve imaging speed and multicolor excitation. He described multiphoton light-sheet microscopy, combining two-photon excited fluorescence with orthogonal illumination, and demonstrated its performance in maintaining high spatial resolution deep inside biological tissues, as well as high acquisition speed and low phototoxicity. In addition, he presented a strategy based on wavelength mixing to perform optimal and simultaneous two-photon excitation of three chromophores with distinct absorption spectra. These approaches open new opportunities for live, multicolor, multidimensional and multiscale imaging, illustrated by imaging Brainbow-labeled tissues, heart dynamic and early fly and zebrafish embryonic development.

Optical imaging of the human heart
Bastiaan Boukens (Washington University)
Mathematical modeling has an important role in cardiology: in forward and inverse calculations between local cardiac events and the body surface ECG, and in understanding complex atrial or ventricular arrhythmias. In order to develop and optimize an accurate mathematical model, experimental data is required. Dr. Boukens described optical imaging techiniques which have enabled the recording of epicardial and transmural activation and repolarization patterns with a high spatial resolution. He showed how optical imaging allows scientists to relate the metabolic state and ionic homeostasis with cardiac electrophysiology by measuring simultaneously membrane voltage and Ca2+ and Na+ with fluorescent indicators or NADH, which has its own fluorescent spectrum. Several optical imaging modalities were discussed, with applications to studying human non-failing and failing hearts.

Studying mammalian embryonic development through optical imaging
Irina Larina (Baylor College of Medicine)
Understanding the nature and mechanism of congenital defects of different organ systems in humans has heavily relied on the analysis of the corresponding mutant phenotypes in mouse models. Thus, developing novel approaches for live mouse embryonic imaging and analysis is of extreme importance. Dr. Larina described how optical imaging can be used to visualize live developing mouse embryonic structures at different embryonic stages. She highlighted two optical imaging approach - fluorescence microscopy of vital reporters and optical coherence tomography - and discussed how these methods can be utilized for structural imaging of early mouse embryos

in static culture, 4D cardiodynamic and blood flow analysis, and in utero embryonic imaging at later stages of gestation. She demonstrated how these methods can be used to assess structural and functional birth defects in mouse models. Dr. Larina concluded by focusing on future trends and existing challenges in data interpretation, analysis and modeling.

Cellular and Network Simulation of Microcirculatory Flow Dynamics
Jonathan Freund (University of Illinois at Urbana-Champagne
The time-dependent dynamics of microcirculatory blood flow are well understood to couple dynamically with other mechanisms in developmental, disease processes, and potential therapies. In his talk, Dr. Freund described the advanced simulation techniques he uses to study such flows. He presented an overview of a flow solver with fully detailed cellular descriptions of the flowing blood, along with multiple applications. Additionally, he described a reduced viscous-limit model for flow in elastic vessel networks, motivated by microscopy data. Dr. Freund highlighted results regarding the shear-stress footprints of passing cells and how they might constitute important mechanotriggers, the transport of therapeutic magnetic nanoparticles by a cellular blood flow, and the capacitive role of vascular elasticity at the onset of circulation in the developing zebrafish.

WEDNESDAY, MARCH 19, 2014

Multiscale modeling of atrial fibrillation
Oleg Aslandi (Biomedical Engineering, King's College of London)
Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting over six million people in the US and imposing a huge healthcare burden on modern society. Despite a vast amount of data collected from patients and ex-vivo protein-to-organ scales experiments, the complex mechanisms of AF onset are poorly understood and clinical treatment remain suboptimal.

In this talk, Dr. Aslandi presented biophysical models that provide a quantitative framework for integrating multimodal and multiscale data and simulating the arrhythmogenic atrial dynamics arising across multiple scales. Dr. Aslandi has developed 3D models of the atria that integrate heterogeneous electrophysiological (ion channel, gap junction, action potential) and structural characteristics (atrial morphology, fiber orientation, fibrosis) and their remodeling during AF progression. Simulations of the model enable: (1) dissection of key determinants of atrial substrate for re-entrant waves maintaining AF; (2) exploring how evolution of this substrate due to progressive remodeling self-perpetuates AF; and (3) quantifying the effects of antiarrhythmic drugs on the evolution of the substrate. Model predictions are validated against available atrial mapping data on canines and humans, and may provide novel insights into AF mechanisms and clinical treatments.
A comparison of electrocardiographic imaging of cardiac potential fields of the timing of the EDL source
Adriaan van Oosterom (Medical Faculty, Radboud University Nijmegen)
The dynamics of the contraction of the cardiac muscle are initiated and accompanied by the flow of electric currents. The observed time course of the potential differences between any two locations inside the thorax, or on its surface, is referred to as an electrocardiogram (ECG). The visualization of ECG time series by means of maps has led to the search for methods of displaying

their interpretation as maps; thus emphasizing the spatial character of cardiac electric sources. The interpretation of the ECG amount to solving an inverse problem seeking: (1) maps of timing of the activation and recovery of the myocytes; (2) maps of the potential field on a surface outside but close to myocardium.

In this talk, Dr. van Oosterom presented the derivation of the models for these inverse problems: the double layer current source model (S1), and the pericardial potential distribution model (S2). The double layer current source model is based on electrophysiology and requires non-linear parameter estimation to infer the timing maps. The pericardial potential distribution model is based on biophysics and the inference of the potential fields maps from ECG recording reduces to a linear regression problem. Dr. van Oosterom concluded the talk with several examples of the maps generated using the two models presented.

How can we use dynamic models in inverse bioelectric problems?
Dana H. Brooks (ECE Department, Northeastern University)
Cardiac and brain bioelectric forward problems can be modeled accurately as quasi-static, implying that torso or scalp surface measurements depend on the spatial distribution of the respective sources independently at each time instant. However, in both cases the time series of the sources are in large part a function of intrinsic electrophysiological dynamics, and as such, exhibit strong and complex temporal correlations.

In this talk Dr. Brooks presented several approaches for dynamic modeling in inverse bioelectric problems, with application to electrocardiography. He described three standard methods (Joint regularization, Statistical temporal decorrelation, and State-space dynamical model) and described how these are related through their assumptions about the spatiotemporal covariance structure. Dr. Brooks then presented results with clinically measured data using a new method that incorporates a non-linear temporal model (temporally constrained low order signal space approximation). Finally, he used a manifold learning approach based on Laplacian Eigenmaps, to illustrate non-linear dynamic structures in measured EEG signals.

Forward modeling of medical imaging systems
Paul Kinahan (Imaging Research Laboratory, University of Washington)
In medical imaging, the true underlying property of interest is unknown. A single image provides little to no insight into the impact of confounding factors (statistical noise, biological variability, patient motion, detector resolution, etc). Some of these factors can be quantified by scanning various phantoms. Physical phantoms, however, cannot capture variability due to patient physiology.

In this talk, Dr. Kinahan spoke about how one may use forward modeling of imaging systems to examine and improve the performance of medical imaging systems. Forward modeling of medical imaging systems is a tool for testing system understanding, estimating gaps in what can't be measured directly, evaluating scanner designs before construction, repeating studies to evaluate statistical performance, and analyzing virtual clinical trials. Dr. Kinahan illustrated the use of forward modeling for optimizing and testing various configurations of a PET/CT scanner prior to

its construction. A second application of forward modeling concerning the image reconstruction inverse problem was studied, and it was demonstrated that the source position affects the quality of the image and must be built into the forward model of any imaging system. Dr. Kinahan concluded the talk with the use of forward modeling in the development of virtual clinical trials with application to digital breast tomosynthesis, detectability of change in PET images, and the incorporation of biology in the input 18F-FMISO imaging of hypoxia with PET.

Measurement of cancer heterogeneity with positron emission tomography data
Finbarr O'Sullivan (Department of Statistics, University College Cork)
PET/CT is widely used clinically to diagnose and monitor cancer patients. Cancer is a heterogeneous process and the quantitation of this aspect is of interest. However, the scales of heterogeneity that can be measured for imaging are severely limited by the image resolution.
In this talk, Dr. O'Sullivan presented alternative approaches to measuring heterogeneity in cancer imaging with examples from PET imaging studies in patients with sarcoma, brain, and breast cancer. To further highlight the heterogeneous nature of a cancer, he showed clinical data on sarcoma demonstrating the variability of cancer tumors across patients. Dr. O'Sullivan developed a statistical model for homogeneous tumors, and the heterogeneity coefficient of a specific patient is quantified as a departure from the homogeneous model when the fitting is done on the patient data. A Cox survival analysis incorporating the novel heterogeneity measure as predictor among others was done on a cohort of sarcoma patients, and demonstrated that the heterogeneity measure is the most relevant of the included predictors of patient outcome in sarcoma. He also presented a spatial spheroid model of tumor growth that lead to a simplified tumor level-set visualization.

Methods for detecting and analyzing large scale networks in human brain using fMRI data
Gabriele Lohmann (University Clinic Tubingen)
Standard analyses of functional MRI data aim at locating activation areas in the brain. Traditional approaches have regarded the brain as a stationary and univariate entity. However, the brain operates as a complex and dynamic network, and massively multivariate techniques are becoming increasingly important in fMRI. Dr. Lohmann presented two new techniques that aim at understanding the complex networks in the brain. Despite the overwhelming number of neurons in the brain, these mostly organize into small world networks; thus, techniques such as the eigenvector centrality mapping (ECM) that are used to understand the World Wide Web should be applicable to understand the organization of the brain.

Dr. Lohmann's team applied the ECM approach to fMRI data in task-absent conditions where subjects were in states of hunger or satiety. Using linear correlations and spectral coherence between time series as similarity measures, they showed that eigenvector centrality is modulated by the state the subject was in. It is also computationally efficient for capturing the neural architecture of the activated regions on a voxel-wise level. She then used Non-negative Matrix Factorization (NMF) based on correlation matrices of fMRI time series to identify small activated networks in the brain in a resting state experiment. The mean matrices resulting from the NMF factorizations were then used in combination with the GINI coefficients to understand how the identified small networks interacted, and revealed overlaps between networks. Dr. Lohmann

concluded the talk by discussing the open question regarding how the new methods may be utilized to elucidate dynamics brain function.

THURSDAY, MARCH 20, 2014

Multi-Scale Modeling and Imaging of the Failing Heart: From Mouse to Human
Andrew McCulloch (University of California San Diego)
To understand the heart and why it fails, it is important to understand it at multiple scales. Dr. McCulloch spoke about models have been developed that have included the biomechanical, electrophysiological, and regulatory functions as well as structurally across physical scales of organization from molecule to organ system. These models have been informed by data from multi-scale imaging studies, where patient-specific data can be obtained. Dr. McCulloch's group has developed novel subcellular models that show how the three-dimensional architecture of the transverse tubule system and calcium release units affect the dynamics and heterogeneity of calcium signaling in cardiac myocytes. This modeling work incorporated the subcellular observation that almost all calcium is released from the sarcoplasmic reticulum during a spark, and that this depletion can prolong sparks. In order to understand heart failure it is important to understand calcium conduction.

Dr. McCulloch discussed his group's use of mice as models for heart failure. Experimental studies in mice at multiple scales including in-vivo MRI have allowed his group to validate models and identify integrative mechanisms of disease as well as therapy. The vinculin protein was identified as particularly important for shaping the heart's cardiac fiber orientation. Using knockout mice, Dr. McCulloch's group examined irregular fiber orientations and how they affect heart function. The key question his group was looking to answer was why cardiac resynchronization therapy (CRT) has a low success rate. In order to predict the success of CRT, it was demonstrated that three dimensional patient-specific imaging data combined with a multi-scale biophysical model is needed.

Multi-Modality data fusion for cardiac biophysical modeling
Kawal Rhode (Kings College London)
There now exist a multitude of data modalities available for visualizing and measuring cardiac physiology. Dr. Rhode discussed the use of biophysical modeling and imaging for managing patients with heart disorders including atrial fibrillation, heart failure, and ventricular tachycardia. Use of imaging and modeling can help with patient selection for procedures, therapy planning, and therapy guidance. A number of imaging modalities and observational tools are used which give complementary information. However, the availability of these tools has not yet led to improvement in patient outcome. The difficulty lies in the integration of these types of information to get useful representations of each patient.

Dr. Rhode discussed work to this end, including co-registration of images across the various imaging modalities in common use. The different types of measurements are combined in order to obtain integrated representations of the patients. For instance, echo compounding is used to co-register images of the heart that come from different views. This information is combined with

doppler diffusion to obtain three dimensional flow vectors in the heart. One of the main difficulties in performing such co-registration is the inherent difference in the contrast properties across image modalities. Dr. Rhode presented work performed by his group aimed at circumventing such a difficulty. Through the use of data and modeling, accurate representations of isochrone maps in patients can be produced.

Three Dimensional Conduction During Atrial Fibrillation (a modeling approach)
Ali Gharaviri (Maastricht University)
Recently, cardiac researchers have worked to determine how the structure of the heart affects its conduction. In this talk, Dr. Gharaviri elaborated on how the three-dimensional conduction profile of the heart affects atrial fibrillation (AF) and the effect that conduction has on stability. AF features spiral waves of electrical activity propagation. The proposed mechanisms of AF spiral waves are ectopic focal discharges, multiple wavelet re-entries, or single reentrant circuits, though it is unclear which structural changes cause these waves. Atrial fibrillation has been known to become more stable over time, and there are several possible mechanisms to explain this phenotype, consistent with its proposed mechanisms. Dr. Gharaviri's group focused on the effect that varying atrial thickness could have on atrial fibrillation, since one of the main mechanisms contributing to the stability of AF is structural remodeling of the atria. Varying atrial thickness was shown to have an effect on AF conduction, since it affects the fiber architecture.

Still, these models did not explain new experimental studies that suggested that the development of AF is associated with increased conduction between the sub-epicardial layer and end endocardial bundle network. Based on these studies, Dr. Gharviri introduced a new model for AF involving "epicardial breakthrough waves," where waves in the sub-epicardial layer propagate outward thereby affecting AF.

Imaging and Modeling Panel: From image to image analysis to physical model (and back): comparing mathematical/physical models with experimental images, designing the modeling/imaging pipeline for validation, prediction
Moderator: Kristin Swanson
Panel: Andrew McCulloch, Aichi Chen, Ali Khan, Natasha Lepore, Lei Wang, Finbarr O'Sullivan
This panel discussion focused on three interrelated aspects for how mathematical modeling is used in biological studies. The first aspect was how modeling is used as a data discovery tool. Mathematical modeling is widely used to extract data from images through the use of various algorithms. For example, modeling is useful for extracting data out of biomedical images. The second aspect was inverse problems, where data can be looked at in the context of models from which parameters may be extracted. The final aspect was on the use of modeling for making predictions.

It was noted that researchers generally work on one of these three aspects of modeling, and that there were inherent limitations to such an approach. In particular, these three aspects of modeling have heavy overlap, and there is a need for interchange of ideas and for collaboration between researchers who work in different related areas. The discussion then shifted to data sharing, for

more efficient use of scientific resources. The challenges of data sharing are numerous, and extend beyond the technological. The root question was how science could make data sharing less thankless, and property assign credit and protect intellectual property. While it was generally agreed that data sharing is an ideal to work towards, it was acknowledged that the hurdles to data sharing are numerous and not easily overcome.

Organization and variability of the human cerebral cortex from global to local quantification and modeling

Olivier Coulon (Aix-Marseille University)

The variability of the cerebral cortex across individuals poses several challenges to researchers. It is an obstacle to inter-subject registration when performing neuroimaging group studies. It also makes it difficult to define a normal state and discriminate such state from abnormal states. Particular landmarks of the cerebral cortex are visible in Magnetic Resonance Imaging (MRI) acquisitions, and there is considerable debate over whether these landmarks are representative of cortical organization and architecture.

In this talk Dr. Coulon presented methods used for studying cortical organization and variability at both global and microscopic spatial scales. At the global level, cortical surfaces were mapped to spherical domains to aid in comparison across subjects. The difficulty in doing this procedure lies in the variability of the sulci across individuals, but particular anatomic poles were identified and an algorithm named HIPHOP was presented to perform this alignment. Sulcal variability was shown to relate to differences in function, as various stereotyped folding patterns are observed. There is the potential to extend these results using future equipment that is able to correlate functional information with micro-scale anatomy in vivo.

Multimodal Neuroimaging Markers for Neuropsychiatric Disorders

Lei Wang (Northwestern University)

In this talk, Dr. Wang described some of his group's recent development of computational anatomy tools for the study of brain structure and function with focus on clinical applications of imaging. The first clinical application was the identification of biomarkers for specific disorders like Alzheimer's Disease (AD). He discussed how abnormal structure and abnormal brain activity do not always overlap, and the effect of disease on structure and function is not always 1:1. For investigation of such problems, many different types of data need to be fused together.

In particular, AD involves degeneration of both grey and white matter. A main theoretical difficulty of fusing together different sources is registration, and Dr. Wang discussed his groups LDDMM method for registration that is able to preserve brain features without blurring, as opposed to methods involving population averages. A main contribution of LDDMM is to show how to treat high-accuracy regions different from low-accuracy regions in registration. Using these tools, his group was able to investigate the relationship between cortical thickness and geometry in AD patients, in order to extrapolate a predictor for the likelihood of AD. Using these tools, his group also investigated the relationship between cortical thickness and metabolism, comparing the thinning for AD patients and MCI patients, and how the metabolism of these two groups changes with progression of disease.

Crossing scales in the brain from functional MRI to synaptic function
Alan Koretsky (NIH)
Dr. Koretsky gave a talk about recent developments in functional MRI technology that have allowed researchers to probe the brain noninvasively at near cellular-level resolution. Such advances in technology are allowing scientists to measure changes in neural circuits that result from plasticity. Of particular interest are the cases of long-range cortical rearrangements that have been detected in the human brain after injury. MRI is now being used to pinpoint precisely sites of synaptic changes where researchers have been able to observe the changes in synaptic weights that occur as result of injury or as compensation for disability such as blindness. In mice, MRI showed that after injury there is an up-regulation of callosal inputs from the uninjured cortex to the cortical representation of the area that becomes denervated.

While the MRI available for rodents is currently stronger, Dr. Koretsky conveyed his optimism that higher-strength MRI will soon be available for humans. The results of the studies he mentioned, taken together, demonstrate that MRI is positioned to begin to give laminar specific information about mechanisms of cortical plasticity. These higher strength machines, along with selective use of contrast agents such as manganese, can mark active cells in the cortex to generate activation maps or trace neuronal connections. There is also the potential of using strontium in order to see synaptic-scale events occurring in high resolution. Lastly, he noted that while MRI is improving, it is still limited in the fact that is measuring neurovascular coupling. In order to fully understand the results from MRI, future work will be needed to understand neurovascular coupling.

FRIDAY, MARCH 21, 2014

Building and Interacting with The Virtual Brain
Randy McIntosh (University of Toronto)
Dr. McIntosh gave an introduction to The Virtual Brain (TVB, thevirtualbrain.org), an international project that uses real neuroimaging data to construct a simulation of the human brain. The Virtual Brain is a whole-network approach to study the brain, where the idea is that all of brain function is the result of its networks working together to instantiate mental function. Using anatomic data, local-scale dynamics can be related to large-scale activity patterns. The result of these simulations is directly comparable to empirical data such as EEG or fMRI.

Dr. McIntosh described how The Virtual Brain was used to explore the role of noise in the brain. Noise helps the brain explore many possible different configurations, and it was found that the system being at the edge of criticality is important with noise allowing the brain to explore different states. The noise is important for function, and the level of noise in individuals changes with maturation. Finally, Dr. McIntosh described a live art-experiment where participants were able to modify their surrounds through their own brain patterns. Through this visually stunning display, sex differences in brain activity were demonstrated.

Integrating multimodal quantitative MRI and histology for improving surgical treatment of epilepsy

Ali Khan (National Heart and lung Institute, Imperial College London)

Surgical excision of the affected brain region is often necessary to achieve seizure control. However, precise delineation of the seizure onset zone can be challenging, and can lead to poor surgical outcomes when incorrect. In many of these cases, the underlying pathology consists of subtle architectural abnormalities at the microscopic scale.

In this talk, Dr. Khan presented an approach integrating in vivo MRI modalities that can probe tissue microarchitecture, along with validation against histology to improve delineation of these lesions at a macroscopic scale. This method is based on correlating quantitative relaxometry and diffusion imaging of temporal lobe epilepsy patients with histology of surgical specimens. Dr. Khan's approach to the problem is to develop an objective characterization of neuropathology, a multiscale approach to quantifying cortical architecture, and model the relationship between quantitative MRI and neuropathology. A major challenge of the methodology is aligning the anatomy at vastly different scales and learning the relationship between intrinsic MRI parameters and histological parameters.

Current Topic Workshop: From Within Host Dynamics to the Epidemiology of Infectious Disease

April 7-11, 2014

Organizers: Steve Cantrell (University of Miami), Mary Galinski (Emory University), and Juan Gutierrez (University of Georgia)

Report by: Paul Hurtado, Karly Jacobsen

MONDAY, APRIL 7, 2014

Scientific Overview and Challenges

Eberhard Voit (Georgia Institute of Technology and Emory University)

Dr. Voit started off the workshop with a broad overview of the challenges of infectious disease modeling and the necessity of tackling the largely unsolved problem of bridging levels of organization. A spectrum of spatial scales from complicated metabolic pathways to ecosystems needs to be taken into account, and a wide range of temporal time scales presents another significant challenge. He discussed the commonly used technique of separating time scales and how this approach may be problematic for host-pathogen interactions. Potential solutions for bridging the gap were offered such as beginning with mesoscopic models, using hybrid agent-based models, concatenating models from different levels, creating super template models, and reusing modules from one level to another. He further mentioned the enormous challenge that heterogeneous data presents. A summary of the program of talks for the week was provided, indicating how the abstract, data-driven and multi-scale models to be presented will contribute to the themes of the workshop. He concluded by emphasizing the importance of bidirectional communication and transdisciplinary education.

Deterministic within-host viral dynamics
Sergei Pilyugin (University of Florida)
Dr. Pilyugin discussed deterministic within-host viral dynamics in the context of antiviral treatments. He considered a variant of the standard Perelson et al. within-host model that included direct cell-to-cell transmission of the virus. Motivated by reverse transcriptase and protease inhibitors for HIV, two types of antiviral treatments were incorporated into the model. The effective basic reproductive number was calculated in the case of constant treatment efficacies. Dr. Pilyugin also employed Floquet theory to analyze time-periodic efficacies corresponding to the clinically relevant scenario of a periodic treatment regimen. Using a small perturbation approach he found that the perturbation can both stabilize and destabilize the system. In particular, treatment success may depend on the phase difference between the efficacies of the two inhibitors. Numerical simulations also demonstrated the dependence of R_0 on the phase difference in the case of large perturbations where anti-phase treatments were successful while in-phase treatment was not.

A mathematical model for coupling within-host and between-host dynamics in an environmentally-driven infectious disease
Zhilan Feng (Purdue University)
Dr. Feng presented a mathematical model for *toxoplasma gondii* that couples the within-host virus dynamics with the between-host population dynamics. The model is used to study questions related to the evolution of parasite virulence and whether a conflict exists between natural selection at the within- and between- host levels. Differing time scales of the immunological and epidemiological processes allow the models to be coupled by finding the within-host fast system endemic steady state and putting the equilibrium value of the virus population into the between-host system. Stability analysis of the infection-free equilibrium (IFE) for the between-host system revealed that the IFE can be locally asymptotically stable even in the case that the between-host basic reproduction number is greater than one, given that the within-host system reproduction number is less than one. Analysis of the time-separated case was concluded by determining a lower bound for the between-host reproduction number, a threshold below which a backward bifurcation occurs and multiple steady states exist. Dr. Feng used singular perturbation analysis to investigate the dynamical behavior of the full system when the time-scale separation is no longer assumed. Numerical simulations confirmed the existence of multiple steady states. Finally, Dr. Feng discussed the role of the inoculation rate constant and corresponding control implications as well as the mathematical challenge of analyzing the case where the within-host system does not have a globally stable steady state.

Optimal Control and Analysis of a Coupled ODE/PDE Immuno-epidemiological Model
Eric Numfor (University of Tennessee)
Dr. Numfor uses optimal control theory to investigate the impact of giving treatment to HIV-positive individuals via two types of antiretroviral drugs: transmission suppressing drugs and viral production suppressing drugs. The coupled ODE/PDE model translates individual characteristics including immune status and pathogen load to the population level and traces their epidemiological significance. He discussed nesting a within-host model within an epidemiological model through linking mechanisms including a structural variable and coefficients. Dr. Numfor employed

Ekeland's variational principle to prove existence and uniqueness of the optimal control where the objective functional minimized free virus, infected individuals and cost of toxicity. He discussed the importance of sensitivity functions and their relation to the adjoint operators. Finally, Dr. Numfor used a forward-backward sweep iterative method to perform numerical simulations which demonstrated that with control the healthy cell counts remained at high levels for longer compared to no control, the virus population had a lower severity and the between-host model showed no oscillatory behavior and lower maximal prevalence of disease.

Reflections on predation, resources, and the linking of within-host pathogen dynamics to epidemiological processes

Robert Holt (University of Florida)

Dr. Holt spoke about the varied impacts of predation on infectious disease emergence and prevalence and their dependence on assumptions regarding host regulation, acquired immunity, predator functional responses, host heterogeneity and within-host pathogen dynamics. Resource effects both in the presence and absence of an immune class were considered; results indicated that allowing transmission to increase with resources does not alter the impact of predation on disease prevalence but can change conditions for persistence of the infection and the existence of multiple steady states. In the second part of his talk, Dr. Holt considered the host to be a patch colonized by the pathogen and shared results on the basic reproduction number which can be influenced by predation through a decrease in host population size, an increase in host mortality, and an indirect increase in pathogen load by boosting resource availability.

Mathematical model on Malaria with multiple strains of pathogens

Yanyu Xiao (University of Miami)

Dr. Xiao motivated her multi-strain model of malaria by discussing areas where malaria parasite distributions are geographically overlapping as well as evidence that newly transmitted *Plasmodium Falciparum* infections were suppressing patient infections with *Plasmodium Vivax*. First, Dr. Xiao considered stability analyses of both the single strain and double strain models at the within-host level. She then continued to discuss a between-host level double strain model incorporating both human and mosquito populations. A threshold parameter for invasion of one species to another resident species was defined, and a corresponding persistence result was presented in which coexistence of strains was proven possible only if both strains had individual reproduction numbers greater than one and cooperative behavior was also exhibited. In conclusion, coinfection of two malaria strains at the within-host level is generically impossible while at the host population level, co-existence of two cooperating species in a region is possible.

Thresholds for Extinction in Stochastic Models of Infectious Diseases: Importance of Time and Location

Linda Allen (Texas Tech University)

Dr. Allen discussed the importance of time and location in establishing infection in within-host and multi-patch models by relating the next generation matrix from deterministic theory to the expectation matrix of stochastic theory. She first considered the dynamics of the infectious class near the disease free equilibrium in a Markov chain model for an SIR epidemic by a branching process approximation. These results were then extended to a multi-type process through the

expectation matrix with the establishment of a threshold theorem. Applications of the theorem were discussed, including extinction results for species invasion among patches and within-host viral transmission, as well as implications for interventions and control methods. Dr. Allen concluded by discussing the limitations of the theorem and the additional challenge of including decay in the branching process.

TUESDAY, APRIL 8, 2014

Disease invasion of community networks with environmental pathogen movement
Joe Tien (The Ohio State University)
Dr. Tien discussed the interplay of community characteristics and network structure in determining disease invasibility in a general network model with an environmental pathogen. Motivation for the work stems from infectious diseases, such as cholera, where the pathogen can persist in the environment and indirect transmission to humans occurs via contact with the environmental pathogen. Using the next-generation matrix method, Dr. Tien considers the basic reproduction number, R_0, in the limiting case of fast water movement relative to pathogen decay; in this case, R_0 can be expressed as a Laurent series using a small perturbation from the singular graph Laplacian matrix. The singular term in the series is related to the rooted spanning trees of the network and represents averaging based on network structure while the zeroth order term is a generalization of the group inverse of the Laplacian and describes how fluctuations from the average due to network clustering affects invasibility. Dr. Tien considered basic river and star network motifs to illustrate the interesting result that network risk of a patch is highest when inflow rates are large compared to outflow rates. He concluded by discussing biological insights including the identification of the most important patches for implementation of a control measure, the challenges of determining patch risk where demography, infrastructure and socioeconomic status play key roles, and the importance of considering how immunological state affects movement.

Identifiability and interacting scales in modeling disease dynamics
Marisa Eisenberg (University of Michigan)
Dr. Eisenberg discussed parameter identifiability and multiple interacting scales in infectious diseases that provide interesting opportunities for data collection. Identifiability approaches including differential algebra and likelihood profiling were illustrated with her work on modeling cholera and oropharyngeal cancer. Dr. Eisenberg showed that the scaled SIWR model for cholera is structurally identifiable except in the limit as the pathogen lifetime decreases, which allows the relative contributions between the direct and indirect pathways to be determined. Practical identifiability issues were resolved by introducing rainfall data to force environmental transmission in the model for Haiti that allowed forecasting of disease outbreaks. In the second application, Dr. Eisenberg discussed the open questions and data challenges in multiscale modeling of HPV and oropharyngeal cancer. She emphasized that while HPV prevalence data and population level cancer trends are available, the lack of within-host data presents an interesting opportunity for modeling to be useful.

Within-host to population-level modeling of mycoplasmal conjunctivitis in wild birds

Paul Hurtado (The Ohio State University)
Dr. Hurtado introduced the pathogenic bacterium *Mycoplasma gallisepticum,* which jumped from poultry into North American House Finch populations during the early 1990s, and has since been used as a model wildlife disease system in which to study emerging infectious diseases. After discussing individual-level and pathogen-strain-specific variation in this system, Dr. Hurtado presented results obtained by using a within-host dynamic model of pathogen proliferation and the host immune response, which was used to "scale up" from the individual level to the population level by embedding that model in a stochastic process model of individual infectiousness and survival. These results, along with a sensitivity analysis, provided insight into how natural selection might be acting to shape pathogen characteristics (virulence, in particular) in this system. Dr. Hurtado then discussed results from a population-level model of virulence evolution, highlighting the importance of a novel virulence trade-off present in this (and likely many other) systems with mobile hosts. These results highlighted the conceptual challenges to "scaling up" and the utility of addressing questions that span multiple biological scales with multiple models that address particular processes or patterns at different scales.

Coexistence or Replacement of two Subtypes of Influenza
Pauline van den Driessche (University of Victoria)
Dr. van den Driessche introduced a model of influenza A with two subtypes in order to answer the question of why some pandemic subtypes replace the previous subtype while others coexist with the previous subtype. The multi-scale approach modeled influenza drift by formulating a seasonal model and a season-to-season mapping. The seasonal model is age-structured where the susceptibles are grouped by time since last infection, which determines their cross immunity to related strains. The season-to-season mapping takes into account the final size of the epidemic from the previous season, a quantity for which an implicit equation can be derived. Upon introduction of a pandemic, the fraction of susceptibles remaining at the end of the pandemic can be used to calculate the reproduction number of the seasonal influenza following the epidemic, the threshold value determining replacement vs. coexistence of the two subtypes. Numerical simulations indicated that the pandemic subtype replaces the previous subtype for a wider range of cross-immunity as the fraction escaping pandemic decreases.

Transmission of cholera in the far north region of Cameroon - A model-guided exploration
Song Liang (University of Florida)
Dr. Liang discussed a cholera transmission model for Cameroon that incorporated the hydrological process associated with the disease. This work investigated possible factors driving transmission during cholera outbreaks around Lake Chad that occurred in 2010-2011. A wavelet approach demonstrates correlation between cholera and precipitation. Dr. Liang and colleagues built a hydrological network inferred from the landscape and rainfall and imbedded it via coupling of patches where each patch is modeled with an ordinary differential equations compartment model. AIC was used to compare the full model to reduced versions of the model including those without human mobility, pathogen movement, or water storage. The full model performed best; considering predictions of transmission at the health district level, the full model predictability is 90% for floodplain areas and 84% for mountains. The model revealed clear

hydrogeomorphological signatures in the transmission and, in addition, the importance of human movement.

Epidemiology of tick-borne Rickettsia spp.
Holly Gaff (Old Dominion University)
Dr. Gaff began with an overview of tick natural history and pertinent vector biology, including their punctuated life history - eggs, to larvae, to nymphs, to adults with one blood meal per life stage. They survive off-host for months to years at a time between meals, and as a group include both generalists and specialists. Dr. Gaff then discussed tick-borne diseases, which are the most common vector borne disease in the U.S. and second world-wide, are marked by seemingly unpredictable outbreaks, and are expected to increase with climate change. Dr. Gaff then discussed her long-term study of tick, tick-host, and tick-parasite ecology around Hampton Roads, VA. The goals of the study include using field data to improve our understanding of disease transmission, and to inform mathematical and computational models used to determine high-risk areas and best control practices. Dr. Gaff focused this talk on the question of spillover of Rickettsia spp. from their primary tick hosts (which aren't usually human biters) to tick species that more commonly bite humans, and presented evidence that, despite low prevalence, these spillover events do occur and have potential for increased risk to human health.

Crimean Congo Hemorrhagic Fever: Why Do We Need a Model?
Onder Ergonul (Koc University)
Dr. Ergonul began with an overview of viral hemorrhagic fevers (VHFs) including the tick-borne Crimean Congo Hemorrhagic Fever (CCHF) and it's history of outbreaks in people and domestic animals in Turkey and elsewhere in Europe and Asia. Challenges to treating patients include the fact that most are not brought to the hospital until the later stages of severe disease. Since currently available drugs are most effective during the early stages of infection, they have earned a reputation of being ineffective for some doctors accustomed to treating late-stage infections. Vaccines have been developed, but it isn't clear if they are epidemiologically useful or not. Dr. Ergonul went on to discuss the need to model this disease. The benefits include refining existing intuition for the global burden of this disease, forecasting, the public health value of vaccines or other strategies like tick repellents, and (at the individual level) disease treatment.

WEDNESDAY, APRIL 9, 2014

Within-Host and Between-Host Determinants of the Biology of Malaria Infections
John Barnwell (Centers for Disease Control & Prevention)
Dr. Barnwell gave a comprehensive presentation on the complex biology of malaria infections. An historical perspective for the disease was first provided including the discovery of the malaria parasite in 1880, various eradication programs, and the distribution of *P. falciparum* and *P. vivax* in the world today. The Ross-MacDonald mathematical models and theory of malaria transmission were introduced with a discussion of the critical parameters, including the parasite rate, entomological inoculation rate and basic reproduction number. Dr. Barnwell described in detail the *Plasmodium* lifecycle for several parasite species, emphasizing differences in sporogony, liver stage cycle length, incubation period, blood stage periodicity, and gametocyte

development. Malaria infections are variant, strain and species-specific and exhibit behaviors such as recrudescence, superinfection and periodic relapses. Dr. Barnwell's talk highlighted the many layers of complexity of the disease that must be considered with respect to both within-host and between-host frameworks.

Synergistic and antagonistic interactions between bed-nets and vaccines in the control of malaria

Yael Artzy-Randrup (University of Amsterdam)

Dr. Artzy-Randrup began with an overview of malaria immunity, transmission, and the distinction between infection status and disease status. The "peak-shift" phenomenon, whereby changes in disease ecology or control can shift the age of peak prevalence, was also introduced. Such phenomena are important given that age class differences complicate assessment and control of disease at the population level. Dr. Artzy-Randrup then discussed in greater detail the challenges age-structure poses for malaria assessment and control, and the current and expected efficacy of control measures such as treated bed nets and a potential vaccination campaign that would likely be administered as part of existing measles vaccination programs. Dr. Artzy-Randrup then introduced an SIRS model with age structure to more carefully explore different control strategies, including three different vaccines that target different stages of the malaria transmission cycle, and used the model to assess their impacts on disease and infection control. This analysis revealed that these control measures do not have the expected synergistic effects. Under the proposed model an intermediate-effort peak in mortality can occur, which suggests a poorly implemented control campaign could potentially do more harm than good.

The Malaria Host-Pathogen Interaction Center: a Systems Biology Coalition

Mary Galinski (Emory University School of Medicine)

Dr. Galinski began with an historical and broad biological overview of malaria, and how data availability is changing the kinds of questions we can answer about different malaria parasites, their hosts, and their environments. Dr. Galinski then introduced the Malaria Host-Pathogen Interaction Center (MaHPIC) project, which is organized into different "cores" that specialize in generating and sharing data related to malaria parasites, host immune profiling, functional genomics, proteomics, lipidomics, and metabolomics. A central unifying hypothesis of MaHPIC is that the study of non-human primate hosts and their malaria parasites, as model systems, will provide beneficial insights into malarial disease in humans, and address basic science questions about the interactions between malarial parasites and their hosts. Dr. Galinski then gave an overview of the experiments and sample collection protocols, how those samples would be analyzed by different core groups, and how data from those groups would be organized and shared among groups and incorporated into a database that includes access and data visualization tools. This will be the first dual host-parasite database of its kind. Dr. Galinski then concluded with additional discussions of the studies they are planning to conduct, potential clinical applications of this work, and closed by listing additional sources of information about MaHPIC and malaria in general.

Functional genomics of Malaria host-pathogen interaction center

Kevin Lee (Georgia Institute of Technology)

Dr. Lee began with an overview of where his work fit in the broader MaHPIC project, and presented it as an example of the kinds of work undertaken by the Functional Genomics Core. He introduced the drug Pyramethamine and described how it acts to inhibit folate cycling and thus disrupt purine synthesis, thymidine synthesis, and nucleotide production. After describing the transcriptome and metabolome data obtained from controlled drug treatment experiments in a non-human primate, he presented results showing how an analysis of such data can reveal a more detailed look at how those pathways are disrupted. His results also showed additional insights, namely a positive shift in gametocyte levels following drug treatment. The speaker then concluded with a summary of his findings regarding the effects of the drug on host and parasites, and pointed to unexpected observations such as the gametocyte shift as an example of how this in-depth approach to studying the host-parasite interaction is likely to provide new insights into malarial disease.

Systems-scale and integrative "omic" analysis of host-pathogen interactions in malaria
Mark Styczynski (Georgia Institute of Technology)
Dr. Styczynski first introduced the project goals of the Computational Analysis and Mathematical Modeling core, and the motivations for taking an integrative "omics" approach to modelling the host-pathogen interaction in malaria. He followed with a graph theory and network analysis overview on the challenges of using things like Bayesian network approaches that employ Directed Acyclic Graphs to construct correlative models. He then discussed an alternative approach that uses tree-like Bayesian networks, which can speed up computations by two orders of magnitude. The cost of this speed-up is the rigid tree structure of the models. The speaker then discussed different algorithms for implementing these models, and concluded with an overview of research directions for improving these tools.

Modeling The Blood Stage Infection In Malaria: Advantages Of Discrete Versus Continuous Approaches
Luis Fonseca (Georgia Institute of Technology and Emory University)
Dr. Fonseca began with an overview of the malaria life cycle and the significance of the blood-stage of the parasite life cycle. This stage involves interactions between malarial merozoites, the erythropoetic system, and the immune system. This is also a key stage in determining the trajectory of the infection. The age structure of the red blood cell (RBC) population -- and hence the dynamics of RBC generation, maturation, infection, and death – is critical at this stage. However, which modelling framework captures these dynamics best is unclear. The goal of this work, therefore, was to ascertain the most appropriate modelling framework for the blood-stage of infection. An ODE, DDE and a discrete time recursive model were compared. By comparing RBC maturation times, rates of amplification and differentiation, the overall best model was the discrete time recursive equation. This framework was suited to both the computational nature of these models, and provides a base for more refined models as more detailed information becomes available through the MaHPIC project.

Insights into Plasmodium vivax from spatial maps of human gene polymorphisms: Duffy blood group and G6PD deficiency
Rosalind Howes (University of Oxford)

The goal of this talk was to demonstrate the role of spatial models in supporting public health decision makers and to demonstrate how information about the host (human) genetic landscape can inform infectious disease epidemiology. Dr. Howes began by introducing the Malaria Atlas Project (MAP), founded in 2005, which produces maps to inform public health policy and research. The goal was to map incidence of of the dominant malarias (*P. vivax* and *P. falciparum*) as well as entomological inoculation rates (EIR), vector distributions, and human genetic diversity including Duffy Blood Group types and inherited blood disorders like G6PD deficiency (the drug Primiquin causes adverse reactions in patients with G6PD deficiency, and there are currently no point-of-care diagnostics for the condition). Dr. Howes discussed the methodology used in generating such maps, and challenges to mapping complex disorders with multiple underlying causes.

THURSDAY, APRIL 10, 2014

Spatial and Temporal Malaria Risk Profiles
Marcia Castro (Harvard School of Public Health)
Dr. Castro began with an overview of modern frontier expansion into the Brazilian Amazon, the related transformation to agricultural lands, human settlements, and the construction of infrastructure such as roads and dams. These initiatives led to substantial environmental transformation and severe malaria transmission. Dr. Castro focused the remainder of the talk on a specific settlement project. She presented a spatially explicit methodological approach to collect and analyze combined spatial data in order to identify the top risk factors for malaria transmission among roughly 90 covariates. The data ranged from LandsSAT images to field surveys of people in the settlement area. Results of those analyses revealed that determinants vary across space and over time. During the early stages of frontier settlement, environmental factors drive transmission risk, particularly ecosystem transformations that promote larval habitats of *Anopheles darlingi*. Second, following the establishment of agricultural and urban environments, malaria transmission was substantially reduced, and human behavioral factors were the main drivers of infection risk.

Tracking dynamic innate immune responses in experimental malaria infection
Rabindra Tirouvanziam (Emory University)
Dr. Tirouvanziam's talk focused on the dynamic immune response to *P. cynomolgi* infection in experimental infections in non-human primates (NHPs), and the knowledge gaps regarding the involvement of the innate immune system in fighting malaria infections. A goal of the Innate Immune Profiling Core within the Malaria Host Pathogen Interaction Center (MaHPIC) is to fill these knowledge gaps. He provided an overview of the immune response to malaria infection, and methods used to interrogate the immune system both in the field, and in the lab. By tracking functional innate-immune responses to malaria infection in NHPs, he demonstrated how extensive the response by innate immune system is during the course of infection. Dr. Tirouvanziam then discussed how this first-of-its-kind data will be integrated with other omics technologies under MaHPIC and used to build well-informed mathematical models that capture the relevant contributions of both adaptive and innate host immunity. To illustrate how MaHPIC is well-poised to reveal new (i.e., immunologically unexpected) details regarding the dynamic immune response

to malaria infection, he presented an example where it was discovered that neutrophil polarization differed between primary and recurrent infections.

Some effects of host movement in vector-borne disease systems
Chris Cosner (University of Miami)
Dr. Cosner began by introducing a discrete space model framework, and discussed two approaches to spatial modeling of vector-born diseases that parallel Eulerian (location-focused) versus Lagrangian (individual-focused) modelling in physics. He discussed the distinction between commuting (fixed home) and migration (no fixed home) and illustrated these different approaches with examples of classical ecological models. Dr. Cosner then detailed how different models can increase or decrease the basic reproduction number (R0), e.g., by altering contact rates. He also described how these different frameworks compared in a mathematical sense to ecological models like Hanksi-type metapopulation models, and how R0 terms can differ under Eulerian models in other ways, e.g. additive versus multiplicative expressions. These results show the utility of these different model frameworks, and the benefits of comparing similar epidemiological models as well as mathematically similar ecological models.

Flu in ducks and water - a multiscale modeling study
Andreas Handel (University of Georgia)
Dr. Handel began with an overview of the avian influenza life cycle, including the times virus particles spend in the environment outside of their host organisms. Dr. Handel then described how prolonged persistence in the environment plays an important role in transmission between birds, which may lead to a trade-off between low-temperature environmental persistence and higher temperature viability inside infected birds. Dr. Handel then presented an analysis of integro-differential equation models. Using a unique dataset that includes strain-specific environmental virus persistence and viral kinetics from duck challenge experiments, Dr. Handel presented results showing that the environmental persistence phenotype of a strain does not trade off with in-host infection dynamics and virus load. That is, for the phenotypes of environmental persistence and in-host kinetics, there appears to be no trade-off. However, additional results were presented showing that, on a single scale, there was a trade-off with some strains optimizing environmental persistence in water at low temperatures while others reduce sensitivity to increasing temperatures.

Ecological dynamics of a salmon parasite
Mark Lewis (University of Alberta)
As an example of parasites producing unexpected and interesting ecological outcomes, Dr. Lewis discussed an outbreak in the Broughton Archipelago of salmon sea lice, a parasite that is deleterious to juvenile salmon. The speaker described the fieldwork for this project that involved measuring the spatial footprint by sampling down a migration route. Data showed that there was a strong correlation between total farmed lice and average lice on wild salmon. Results of a fitted ODE model demonstrated reduced survival of parasitized juveniles for both pink and chum salmon while Ricker stock-recruitment curves revealed diminished spawning returns for pink salmon only. Dr. Lewis suggested that trophic complexities may explain the difference and, particularly, that sources of predation need to be taken into account. Considering the economic implications of

this work, the speaker concluded by discussing the role of science in policy and the nature of acceptable scientific evidence.

Within host dynamics of HIV and malaria co-infection
Shigui Ruan (University of Miami)
Emphasizing the importance of understanding the basics of the relevant biology prior to model formulation, Dr. Ruan started his talk with an introduction to red and white blood cells and the innate and adaptive immune systems. He further discussed the dynamics of the replication cycle of *P. falciparum* and its affect on the immune system; the details of HIV infection and replication were also given. An ordinary differential equations model was presented for HIV and malaria co-infection in an individual host. Through an equilibrium analysis, Dr. Ruan determined two critical thresholds for the stability of the infection free equilibriums for malaria and HIV, respectively; co-infection occurs in the case that both critical values are exceeded. Numerical simulations were used to explore the affect of an HIV infection introduced in an individual with malaria. In support of experimental findings, the model showed that, in the case of asymptomatic malaria, HIV can induce irregular oscillations in the infected red blood cell and parasite populations. In the case of clinical malaria already exhibiting strong oscillations, HIV contributes to more irregular and more frequent oscillations with increased amplitude, supporting the observations that HIV positive individuals are more likely to have severe malaria and prolonged fever. Dr. Ruan concluded by discussing the need for antimalarial chemotherapy to be combined with administration of antiretrovirals.

Systems Biology of Epidemiology From Genes to Environment
Juan Gutierrez (University of Georgia)
Dr. Gutierrez presented a unified framework for within-host dynamics and epidemiological processes through a "systems biology" approach, arising from the cascade of molecular signaling involved in the within-host dynamics. The multi-scale approach links molecular data to the cellular level by using omics data to quantify the rate of change of gene expression and relates it to the rate of a change of a reaction mediated by that gene. Further linking to the next level involves determination of the transcriptional profile of certain cells and the use of this signature to measure individual populations of immune cells. Continuing to the next level, he discussed calculation of the basic propagation number and the use of diffusion on a low dimensional manifold to investigate between-host dynamics. The talk concluded with an outline of implementation of the model and the potential of building the quantification process from cells to continent.

FRIDAY, APRIL 11, 2014

Parallels between disease and metapopulation dynamics
Alan Hastings (University of California, Davis)
Dr. Hastings began with an overview of habitat occupancy models in ecology, and their similarity to infectious disease models -- the hosts are the habitat, and occupancy status is analogous to infectious status. This was further illustrated by showing how the simple SI model is exactly the Levins metapopulation model, and by comparing the biological assumptions behind each model. Dr. Hastings then provided an overview of where these assumptions have been relaxed in the

ecological literature and the implications of those results for theoretical epidemiology. He began by posing a common parameter estimation problem, estimating the infectious period, and how this is a challenge in a more general modelling framework where the distribution of that period across hosts (or analogously, across, patches) isn't a simple iid exponential distribution. He mentioned a recent paper by Matts Gyllenberg and Ilka Hanksi in Theoretical Population Biology that addresses this issue. Dr. Hastings then gave an overview of how others have dealt with incorporating explicit consideration of population size within patches (analogous to incorporating within-host pathogen load), difference in patch quality (analogous to host heterogeneity), and more recent work looking at multispecies models that could provide a framework for thinking about coinfection models. These comparisons highlighted the extensive overlap between disease dynamics models that incorporate within-host dynamics, and metapopulation or metacommunity dynamics models.

Interference particles as resistance-proof antiviral therapy
Igor Rouzine (University of California, San Francisco)
Dr. Rouzine began with a brief overview of the host-parasite interaction as a multiscale system with between-scale feedbacks. The focus of this talk was modelling cell-level dynamics with feedback from higher levels. He then introduced the potential therapeutic use of these therapeutic interference particles (TIPs), which are functionally dead virus particles that disrupt normal viral replication. Dr. Rouzine described how others have modelled their potential use against HIV infections, where cells are either infected or co-infected with HIV and TIPs. Dr. Rouzine then presented an SIR model with these treatments built in, and considered evolution of resistance against TIP. The results suggest that the evolution of resistance against TIP will reduce HIV fitness in-host, but will increase transmission-based fitness which implies resistant strains could evolve on a fast enough time scale to pose a public health concern, although spread is also hampered by coinfection with sensitive strains.

The molecular epidemiology of P. vivax in Papua New Guinea
Ivo Mueller (Walter and Eliza Hall Institute of Medical Research)
Dr. Mueller began by focusing on *P. vivax*, as there is more rapid acquisition of immunity to *P. vivax* than to *P. falciparum*. *P. vivax* is also important for comparison with the functionally similar *P. cynomolgi* used in animal models. Dr. Mueller presented results from cohort study of children age 1-3, which showed that they experience 2.5-times as many genetically distinct *P. vivax* infections than *P. falciparum* infections. Children with the highest exposure show fastest decrease in their incidence of clinical *P. vivax* episodes. In *P. falciparum*, where immune acquisition is limited, children with high exposure have the highest risk of illness. Dr. Mueller also presented work showing that 60% (wet season) to 80% (dry season) of bloodstage *P. vivax* infections are caused by relapse in the study population, with similar percentages arising from models of *P. vivax* infections in children age 1-3. This suggests relapses contribute significantly to the higher molecular force of bloodstage infections with *P. vivax* and hence more rapid acquisition of immunity.

Spring Emphasis Semester Workshop 4: Analysis and Visualization of Large Collections of Imaging Data

April 21-24, 2014
Organizers: Chandrajit Bajaj (University of Texas), Philipp Keller (Howard Hughes Medical Institute), Mauro Maggioni (Duke University), and Allen Tannenbaum (Stony Brook University)
Report by: Marc Sturrock and Kimberly Fessel

MONDAY, APRIL 21, 2014

2D and 3D Imaging of Entire cells and Tissues at Macromolecular Resolution by Advanced Electron Microscopic Approaches
Manfred Auer (Lawrence Berkeley National Laboratory)
Dr. Auer began his talk by informing the audience that the traditional schematic view of the eukaryotic cell is over-simplified. He went on to show a range of high-resolution images from his lab that revealed the full complexity of the cell, emphasizing the need for a "theoretical biology". He stated the need to determine information such as 3D organization, subcellular location (e.g. with respect to ultrastructural landmarks) and their interaction with other proteins, the cytoskeleton and organelles and any changes of these characteristics during embryonic development, as part of their physiological function or during pathogenesis. Dr. Auer's talk employed many biological examples, including inner ear hair cells and related tissues central to hearing, mammary gland development and breast cancer, as well as microbial communities. He illustrated the power of modern 2D and 3D electron microscopy imaging, including widefield montaging TEM, TEM tomography as well as Focused Ion Beam Scanning Electron Microscopy (FIB/SEM), and Serial Block Face (SBF) SEM. The latter two techniques were shown to yield macromolecular insight into the 3D organization of entire cells and tissues, and have significant potential to shed new light on to a range of biological processes. As an example, he showed evidence of the cytoskeleton tunneling through the nucleus, a phenomenon that has never been observed before. Naturally, there are certain challenges that come with such promising new imaging techniques. Dr. Auer mentioned that while it is now possible to obtain 10k by 10k by 10k voxel data sets (with 32k x 32k x 32k imminent), the computational capabilities do not currently exist to deal with such terabytes of data, in terms of visualization and quantitative analysis.

Extracing large networks from connectomes
Robert Marc (University of Utah)
Dr. Marc 's talk was primarily about mapping neural neural networks in the brain, retina, and spinal cord. He began by describing the current state of the field of connectomics and the challenges it faces. In order to succeed in mapping out these networks, he stated the need for comprehensive parts lists (vertex types), nanometer scale connection detection (edge types), and millimeter scale network tracing. This requires high-resolution transmission electron microscope (TEM) imaging on a scale not routinely possible. By combining serial sectioning and TEM hardware control, Dr. Marc showed it is possible to create automated TEM (ATEM) imaging of the mammalian retina. He went on to pose the question: How should we build larger connectomes? He stated that currently, it is estimated that 100—1000 TEM systems are underutilized globally – suggesting a possible route to take. Dr. Marc then mentioned the challenges of navigating, exploring, segmenting and annotating the data space for characterization of network motifs. He spoke about the Viking system, a software tool that allows web-compliant delivery of imagery and

collection of markups. Currently, there do not exist reliable, robust tools for automated tracking, so the best strategy has been to use multichannel molecular or activity markers and cell classification to segment and prioritize tracking targets, followed by intensive manual annotation. Dr. Marc spoke about the persistent challenge of the vast scale differences for different neurons in a volume. He then talked in detail about the mammalian retina with the primary message that scaling by platform and automated annotation is critical. Dr. Marc concluded his talk by showing that some key networks in the retina are massive structured hubs.

Optimal mass transport for registration of medical data
Allen Tannenbaum (Stony Brook University)
Dr. Tannenbaum spoke on optimal mass transport methods which have recently been applied to various problems in medical imaging analysis, including registration and anatomical shape. Dr. Tannenbaum spoke about the history of the mass transport problem, which was first formulated by Gaspar Monge in 1781, and concerned finding the optimal way - in the sense of minimal transportation cost - of moving a pile of soil from one site to another. He spoke about how this problem was given a modern formulation in the work of Kantorovich, and is now known as the "Monge-Kantorovich problem." He also talked about the registration problem, which is one of the great challenges that must be addressed in order to make image-guided surgery a practical reality. He described registration as the process of establishing a common geometric reference frame between two or more data sets obtained by possibly different imaging modalities. The methods he introduced have been included in software packages, e.g., the 3D Slicer of the Harvard Medical School. He then described some of the key issues in medical imaging, and how optimal mass transport can be used to shed some light on the solution of these problems. He concluded by talking about applications including left atrial fibrillation, traumatic brain injury, and tumor growth models, while noting that very fast implementations using GPUs are possible.

Representation theoretic patterns in three dimensional cryo-electron microscopy
Ronny Hadani (University of Texas at Austin)
Dr. Hadani spoke on the subject of three dimensional cryo-electron microscopy (or 3D cryo-EM, for short). This is the problem of determining the three dimensional structure of a large molecule from a set of images (taken by an electron microscope) of randomly oriented and positioned identical molecular particles which are frozen in a thin layer of ice. Dr. Hadani explained that a solution to this problem is of particular interest, since it could yield a potentially general technique that does not require crystallization or other special preparation stages. He explained that present approaches to the problem fail with particles that are too small, cryo-EM images that are too noisy, or such images at resolutions where the signal-to-noise ratio becomes too small. Dr. Hadani presented the intrinsic reconstitution algorithm, which can be viewed as a basic step for finding the solution of the 3D cryo-EM problem. He noted that this algorithm has a very appealing property in its numerical stability to noise. He then gave an introductory explanation of the mathematical principles underlying this novel algorithmic approach, while touching on how they apply to other fundamental problems in cryo-EM and beyond. He also shed light on the mathematical model underlying the experimental set-up, while describing the main computational problems and technical difficulties that should be resolved as part of three dimensional structure determination from cryo-EM images. He concluded his talk by placing his work in a broader mathematical

perspective, explaining how the intrinsic reconstitution algorithm can be recasted in the framework of categorical optimization, which is a novel paradigm for solving certain types of non-linear optimization problems by characterizing the solution as an object of a category instead of as an element of a set.

Simple signed-distance approach to the measurement of depth in human cerebral cortex
David Ress (University of Texas at Austin)
Dr. Ress began his talk by stating the problem of measuring depth in the human cerebral cortex. He explained that high-resolution functional MRI methods have the potential to resolve depth variations in laminated brain tissues such as in the human cerebral cortex. However, Dr. Ress revealed that it is challenging to create a geometrically logical definition of depth in this highly convoluted topology. Within the gray matter, which is bounded by the gray-white and pial surfaces, a nearest-neighbor Euclidean distance definition from the two surfaces is not satisfactory because of inconsistency between the distances defined from the two surfaces, and a failure to properly follow the dissimilar topologies of the surfaces. A method based on the solution of Laplace's equation between two surfaces has been used, but the usual finite-difference solution methods can suffer from artifacts when the surfaces are discretized onto a grid, particularly in the depths of narrow sulci. Instead, Dr. Ress proposed an alternative approach based on an interpolated signed-distance function that makes direct use of smooth surface representations. He presented a signed distance function, S(x,y,z), defined in two simple ways that are based on Euclidean distance metrics, with the sign determined by the brain volume tissue segmentation. He explained that the signed distance is calculated separately for the gray-white and pial surfaces, which he denoted by Sw and Sp, respectively. He then formed a weighted-distance function, $D(w,x,y,z) = wSw + (1-w)Sp$. He showed that variation of the weighting parameter, $w \in [0,1]$, defines a smooth transition between the two surfaces. He then solved $D(w,x,y,z) = 0$ to obtain w at every grid point within the gray matter domain, and w was defined as a pseudo-potential that smoothly and logically interpolates between the two surfaces; hence, this defining a normalized depth coordinate within the gray matter. To obtain physical distances and gray-matter thickness, he calculated ∇w and traced it from every point on the gray-white surface to the pial surface. The method was applied to four MRI brain anatomies, and yielded visually and quantitatively reasonable measurements of gray matter depth and thickness.

TUESDAY, APRIL 22, 2014

Imaging the brain with heterogeneous data sources
Lawrence Carin (Duke University)
Dr. Carin is interested in using multiple data sources to characterize mental health. He presented a new model for joint analysis of heterogeneous data in which he considers genetic information, fMRI imaging, and various self-answered questionnaires to achieve an overall picture of an individual's mental health status. With these multiple data sources, Dr. Carin attempts to predict questionnaire responses from fMRI and SNP data; likewise, he uses further statistical learning methods to simulate unobserved fMRI images from patients' SNP data and questionnaire answers. Impressively, Dr. Carin's Bayesian model accurately identifies 80% of general mental dysfunction as characterized by independent psychiatric profiles.

Brain microstructure from next generation diffusion MRI
Carl-Fredrik Westin (Harvard Medical School)
While MRI remains a powerful imaging technique utilized by countless doctors for clinical prognoses, fine detail at the level of cellular resolution cannot be determined with the traditional MRI approach because of signal-to-noise difficulties. Dr. Westin discussed new diffusion MRI (dMRI) technologies that can be used to dramatically increase microstructural clarity. While single pulse field gradient (sPFG) experiments are useful for mapping neural tractography, several issues accompany this method including the brain's heterogeneity as well as the infeasibility of the magnetic strength and large gradients needed to obtain clear cellular resolution. These extreme gradients and magnets may prove hazardous and are not available in current clinical settings due to their high costs. Instead, Dr. Westin proposed the use of anisotropic, double PFG to image microscopic structures with commercially available scanners. He also hypothesized that the future of this imaging technique may consist of using even more scanners at various angles or more accurately mapping patient-specific neural connections for surgical resections.

Image-based modeling simulation and visualization
Chris Johnson (University of Utah)
Translating biomedical images into fully functioning computer models encounters many technological challenges from complicated geometric analyses to large-scale data visualization. Dr. Johnson highlighted many of the projects currently underway at the Scientific Computing and Imaging Institute (SCI) that tackle multiple facets of these image-to-model difficulties. With patient-specific data, Dr. Johnson and his group model stress-strain relationships of various joint implants via large-scale finite element algorithms. He anticipates that this work will allow for custom-built hip implants with 3D printing in the near future. Other efforts at the institute include defibrillation simulation for optimal electrode placement and image-based phenotyping. For the latter work, which may eventually be used to diagnose autism or Alzheimer's disease, Dr. Johnson studies shape statistics for classifying control and gene-knockout mice. Researchers at SCI also specialize in software development and have produced programs to segment bodily organs, generate a finite element mesh from medical images, or visualize patient data on mobile devices, to name a few. Lastly, Dr. Johnson discussed his work on uncertainty quantification. Most 3D imaging is presented without error estimates; however, Dr. Johnson presently works to quantify errors directly on medical images and to visually convey the measurement uncertainties to the viewer efficiently.

Mapping behavior to neural anatomy using machine vision and thermogenetics
Kristin Branson (Howard Hughes Medical Institute, Janelia Farm Research Campus)
Dr. Branson stated that the aim of her research group is to understand the relationship between neural anatomy and behavior. Her group performed a high-throughput, thermogenetic screen of 2,200 transgenic lines of Drosophila from the Janelia GAL4 collection, with each GAL4 line driving expression in a different, sparse subset of neurons in the fly nervous system. Using UAS dTrpa1, they selectively activated these sparse subsets of neurons, and measured the behavioral effects. For this screen, her group developed a complete, high-throughput, automated system for measuring the locomotion and social behavior of flies with both breadth and depth. Her group recorded 20,000 videos of groups of flies freely behaving in an open-field walking arena, which

created about 400 TB of raw data. Her group then tracked the flies' body positions and wings using her tracking software, Ctrax. In addition, they made use of the machine learning-based behavior classification system, JAABA (The Janelia Automatic Animal Behavior Annotator), to create 15 behavior classifiers (e.g. walking, grooming, chasing) that take in the trajectories created by Ctrax and output predictions of the flies' behaviors (totaling ~175 billion annotations of fly behavior). For each line of flies, her group computed a set of ~800 behavior statistics, such as the fraction of time spent chasing, or the average speed while walking, summarizing the behavioral effects of activating the targeted neurons in a concise and interpretable manner. Dr. Branson also talked about an additional study that complemented her group's work, namely, the Janelia Fly Light project. This project has imaged the expression pattern of each GAL4 line, producing image stacks indicating which neurons are likely being activated in each line. By mining the behavior data set in conjunction with the Fly Light imagery data, they have identified novel sets of neurons potentially involved in jumping, female chasing, and wing flicking behavior.

Geometric multiscale methods and models in high dimensions
Mauro Maggioni (Duke University)
Dr Maggioni began his talk by reminding the audience that high-dimensional data appears in a wide variety of applications, from signal processing (e.g. sounds, images), to the study of dynamical systems with high dimensional state spaces, molecular dynamics simulation using stochastic differential equations, to medical, biological and financial data. He then considered a basic model that considered a data point as a sample from a high-dimensional probability distribution. He noted that traditional statistical methods fail in high dimensions due to the curse of dimensionality, and new hypotheses on the structure of data are needed. In particular, he said that the assumption that data, while presented in high-dimensions, is intrinsically low-dimensional, has been verified in many data sets, and has been useful in deriving new methods in statistics and machine learning. He went on to discuss techniques (starting from principle component analysis) that analyze the geometry of data in a robust manner (both with respect to sample size and high-dimensional noise) to estimate the intrinsic dimension, efficiently construct representations of data and dictionaries for it, and to estimate the probability distribution generating the data. In particular he focused on his group's recently developed method called multiscale geometric analysis and also introduced the notion of dictionary learning. He concluded his talk by presenting applications to the detection of anomalies in hyper-spectral images, images, and in regression and classification problems.

Reconstructing development and function of the nervous system using light-sheet microscopy
Philipp J. Keller (Howard Hughes Medical Institute, Janelia Farm Research Campus)
Dr. Keller started his talk by highlighting the interdisciplinary nature of his work and introduced the problem of the development of the embryonic nervous system. He described the overall objective of his research as being to create quantitative experimental techniques to determine the fundamental rules governing neural development, and to systematically link development to the functional activation of circuits in the nervous system. He then presented his group's experimental approach based on light-sheet fluorescence microscopy, an emerging imaging technology that achieves high imaging speed and signal-to-noise ratio, while minimizing light exposure of the specimen (which he noted can be harmful). This unique combination of capabilities makes light-

sheet microscopes indispensable for the long-term in vivo imaging of entire developing organisms. He mentioned that his group is currently designing advanced implementations of scanned light-sheet fluorescence microscopy (such as their SiMView technology framework for simultaneous multiview imaging) to systematically image the early development of entire fruit fly, zebrafish and mouse embryos with cellular resolution. Moreover, he presented strategies for automated large-scale image processing of these multi-terabyte light-sheet microscopy data sets. The combination of experimental and computational approaches allows his group to perform whole-organism functional imaging and to quantitatively analyze developmental lineages and their interrelationships in an entire animal. He stated that in the long-term perspective, they plan to use this information to establish and validate a computational model of the developing nervous system.

Geometric graph-based methods for segmentation of hyperspectral imagery
Andrea Bertozzi (University of California Los Angeles)
Dr. Bertozzi started by reviewing some fundamental concepts of image processing, focusing on the connection between total variation and the Ginzburg-Landau functional. She then showed a few examples of Allen-Cahn equations in image processing. She then discussed the general problem of clustering on graphs and the need to choose an appropriate weight for connecting nodes. Dr. Bertozzi then presented a novel algorithm for segmentation of large datasets with a graph-based structure. The method combines ideas from classical PDE-based image segmentation with fast and accessible linear algebra methods for computing information about the spectrum of the graph Laplacian. She showed how this method managed to successfully cluster the two moon problem, where traditional spectral clustering failed. She then presented results for image processing applications, such as image labeling (where two images of cows were successfully labeled), clustering the MNIST data set, and hyperspectral video segmentation. She showed her group's method compared favorably with other methods in the field. She concluded her talk by revealing an unsupervised version of her method and showed that it performed remarkably well on clustering the 4-9 MNIST data set.

WEDNESDAY, APRIL 23, 2014

Systematic single cell analysis of development
Zhirong Bao (Sloan-Kettering Institute)
The nematode *C. elegans* is a highly valued organism in developmental and neurological research due to its simplicity and consistency. Because these worms have less than one thousand cells, the fate and division history of each cell can be tracked; furthermore, *C. elegans* has been deemed cellularly invariant, which means every wildtype worm exhibits the same cell lineage. Dr. Zhirong Bao takes advantage of this overall simplicity to study cellular origins as well as phenotypic expressions. He has developed an automated computer program for tracking each cell through a time series of fluorescence microscopy images. The method is then used to follow individual cell lines and to study the temporal progress of *C. elegans* development. Though his automated algorithm achieves 99.7% accuracy, errors often propagate throughout the lineages amounting to about 50% error in the fully developed computational worm. He mentioned, however, that combining his program with about 30 minutes of human editing greatly improves his final results. A nice application of his method occurs for studying phenotypic development. Cellular diffusion,

proliferation, and morphogenesis can be examined in both the wildtype and gene-knockout mutants to dictate how genetic variations lead to phenotypic deviations. Lastly, Dr. Bao presented his work on the "emerging mind" of the worm in which he tracks groups of three or four neurons through development to determine neural connections. He will next match up each of these subgroups in hopes of building an atlas to describe how the nervous system of *C. elegans* self-assembles.

Topological representation of large and complex data sets
Gunnar Carlsson (Stanford University)
To begin his talk, Dr. Carlsson gave a brief introduction on the shape characteristics of data, which include properties such as clustering, periodicity, or number of free ends. In broad terms, shape encodes similarity, and the topology of an object or data set refers to a coordinate-free, deformation-invariant, compressed representation of its geometry. Dr. Carlsson explained how topology can be used to represent and measure shape by placing and connecting node clusters over a given data set. A known reference map, such as density estimators, centrality, or principle value decomposition, can be used to delineate each cluster by providing a proper data covering. Dr. Carlsson gave several examples to highlight the benefits of the topological approach including labeling diabetics from glucose-insulin data, recovering small features that indicated different folding trajectories in RNA hairpin data, and predicting morbidity in breast cancer patients from gene-expression profiles. While classical clustering techniques can only break data sets apart by projecting them on lower-dimensional space, topological methods allow the data to retain some of its geometric features and locate critical subpopulations often missed by other processes. Dr. Carlsson also provided an in-depth example for which algebraic topology was used to decompose 2D images into a Klein bottle of representative "patches." This type of technique is referred to as "persistent homology" because useful shape invariants can be found by using persistence on other quantities such as density and centrality.

Data induced challenges in developing chemical imaging for pathology
Rohit Bhargava (University of Illinois at Urbana-Champaign)
Dr. Bhargava specializes in chemical imaging; in particular, he uses spectral data to better classify image features. By combining chemical and structural data, Dr. Bhargava aims to obtain more information from biopsy samples and to improve the accuracy of cancer diagnosis. He has designed an automated mechanical-computational method to help process biopsy samples faster, prevent misdiagnosis errors, aid in treatment projections, and more precisely predict patient prognoses. Dr. Bhargava uses FT-IR (Fourier transform infrared) spectroscopy on a very fine scale to produce images that capture the complete chemical signature of various heterogeneous samples. He then applies signal-processing techniques and other physics-based concepts to reduce sample noise and to recover remarkable image clarity. He also focuses on building specialized instrumentation for his chemical analysis including fast IR spectroscopy. Thus far he has been able to speed up biopsy handing by about 2500 fold; his ultimate goal is to reduce slide-processing time to less than one minute. He would also like to develop techniques to better mine his data for correct prediction of patient outcomes.

High throughput bioimage informatics for neuroscience and cell biology: worm – fly – mouse – human

Hanchuan Peng (Allen Institute for Brain Science)

Dr. Hanchuan Peng has considered many different animal types in his quest for phenotype screening and characterization of neurological connections. He has developed impressive simulation algorithms for image visualization in order to create high-quality, easily accessible atlases of cellular and neuronal architectures. His presentation began with his work on the very simplest animal model: *C. elegans*. Using confocal microscopy and various computational techniques, Dr. Peng has produced the first 3D cell map of the cellularly invariant *C. elegans*. This map has already proved critical for research such as high-throughput localized gene expression analysis. Dr. Peng has also examined the fruitfly brain and has now built a system for standardizing the fly brain space so that data from several thousands of flies can be combined to establish "average" neural network patterns. With this study he has been able to compartmentalize substructures of the brain in a high level of detail and to visualize the connectivity among the neural subsections. Lastly, Dr. Peng commented on his most recent research with a mouse model. Many of the same ideas and methodologies from his fruit fly work still apply for the mouse brain, and he aims to further explore this translation as well as make extensions to the human neural framework in the future.

The Open Microscopy Environment: open image informatics for the biological sciences

Jason Swedlow (University of Dundee)

Dr. Swedlow began his talk by presenting the crux of imaging sciences: while images collected are visually pleasing, they are actually comprised of incredibly rich—and often large—data sets. Managing these data for publication and for resource information can be difficult, which is why Dr. Swedlow and two other scientists founded the Open Microscopy Environment (OME) in 2000. OME aims to serve as a mediary between clients' raw data and successful image analyses. It consists of open-source software that can be used to easily store and manipulate large-scale data, as well as to conveniently share data among collaborators or communities. After providing a brief overview of OME, Dr. Swedlow discussed the organization's many activities including data formatting. The number of formats for image data regularly increases, and OME works to provide translations from specific data formats to more standardized ones. OME is also involved in many different projects and tasks such as data searching, auto-tagging, and figure creation as well as interfacing with programs such as MATLAB, ImageJ, u-track, and FLIMfit. Further, the scientists at OME have developed a remote access server called OMERO which allows OME clients to access data sets from anywhere in the world and to share data amongst themselves without needing to send enormous files via email, say. These data-sharing capabilities are available at any level of privacy thus facilitating multiple tasks such as researching with collaborators, providing students with example images, publishing results, or compiling webpages with interactive figures.

Adaptive mesh representation and processing of biomedical images

Zeyun Yu (University of Wisconsin—Milwaukee)

Image processing remains a highly active area of research due to storage and transmission demands, especially from images taken at ever-increasing resolutions. Traditional pixel- or voxel-based methods are easy to use but often encode large amounts of redundancy, and neither image

compression methods nor superpixel grouping alleviate the resulting data-storage and slow-processing-time issues. Dr. Yu suggests a tradeoff by using the general idea of superpixels but restricting the allowed shape to only be triangular. With this triangulation method, one generally requires much fewer triangles than pixels for image representation, and one automatically achieves an acceptable finite element mesh for further image processing. Using a single triangular size may result in loss of accuracy; however, Dr. Yu adopts an adaptive meshing approach so that a finer mesh is generated for areas of interest, while less significant regions are represented by coarser mesh triangles. Dr. Yu uses Canny's edge detector method to determine the images' local feature measurements and mesh smoothing to improve image triangulation. After an image has undergone compression via mesh triangulation, one would like to find a smooth, continuous function that fits the spatial density of the compressed data for accurate image recovery. Dr. Yu accomplishes this with radial basis functions (RBFs), and while many basis functions are available, he showed the merits of his chosen functions: anisotropic RBFs for data at the triangles' average "face" values. He then concluded his presentation with a live demo of his image processing algorithm and several other recovered image examples, many of which were improved due to the noise smoothing built into Dr. Yu's computational program.

THURSDAY, APRIL 24, 2014

Computational topology, geometry, analysis for quantifying biological form-function relationships using 3D electron microscopy

Chandrajit Bajaj (University of Texas - Austin)

Dr. Bajaj is interested in using imaging to explore how the form of molecular or cellular regions informs functionality. He attempts to obtain images with atomic resolution for highly accurate calculations such as finding molecular binding affinities. Dr. Bajaj detailed a typical binding affinity computation including the use of a linearized Poisson-Boltzmann model, boundary integral formation, and the controlled numerical integration necessary to compute the resulting singular-kernel integrals. He stressed that these calculations must be very exact in order to inform engineering collaborators about likely molecular binding strategies. When building a numerical mesh upon imaging data, one must pay close attention to the topology and geometry of the molecule in question as well as to the spaces between the local molecular neighborhoods. Dr. Bajaj has built an automated process for segmenting molecules while retaining secondary structural details by using generalized Voronoi separation. He then demonstrated the robustness of his finalized segmentation algorithm, which can be used for many spatial scales and can resolve segments up to 80,000 times smaller than the original molecule of interest. Dr. Bajaj also illustrated a practical application of his technique by reconstructing neurons from stacks of TEM (transition electron microscopy) data. He applies his model to this data because he is ultimately interested in small spines on the neuron, which are critical for long-range neural connections, exhibit extreme anisotropic, and vary in spatial scale by four orders of magnitude. Finally, he briefly discussed his current work on uncertainty quantification for molecular interfaces. His results thus far emphasize the importance of including measures of accuracy with imaging data, an aspect of the field that he believes requires more attention.

Solving NMR distance geometry problem by global registration

Yuehaw Khoo (Princeton University)
Nuclear Magnetic Resonance (NMR) has proven to be a powerful tool in delineating molecular structure; however, perfect reconstruction of NMR data remains difficult, especially for larger molecules of interest such as naturally occurring proteins. Yuehaw Khoo proposes a geometric approach for this task and further characterizes the uniqueness of his reconstruction with rigidity theory. Mr. Khoo explained that his work largely consists of solving three subproblems: 1) deconstructing his data into overlapping patches while attempting to retain local rigidity; 2) solving a convex optimization problem on each patch; and 3) stitching his patches back together to reveal the entire molecular structure. He elected to focus on the third step of this process for the remainder of his talk; primarily, he provided techniques for answering, "How can one recover global coordinates from locally optimized coordinates?" Because the two-patch problem has a known solution, one may be tempted to solve with a sequential approach; however, this method quickly accumulates errors and is prone to producing incorrect solutions. Instead, a global cost-minimization scheme should be used; however, the constraints thereby imposed result in a non-convex domain problem with an exponentially large search domain. Mr. Khoo tackles these challenges with several optimization techniques including Gram matrices, semidefinite programming, and perturbation analysis. He concluded by presenting implementations of his algorithm for both simulated and real data of molecules with more than 1000 atoms. Comparison with other approaches showed better or similar accuracy and slightly faster results than current standards.

Two-Stage Method for Salt-and-Pepper Noise Removal Using Statistical Jump Regression Analysis
Jian-Zhou Zhang (Sichuan University)
In his talk, Dr. Zhang presented a novel two-stage method for denoising images. Dr. Zhang reminded the audience that image denoising is a fundamental problem and has been given much attention recently due to the need to denoise medical images. The images he was concerned with denoising were subject to salt-and-pepper noise. The traditional two-stage method applied to this kind of problem first identified the uncorrupted pixels in the image, then estimate the corrupted pixels using the uncorrupted pixels. The drawback of this method is that one either achieves a high peak signal to noise ratio (PSNR) with high computational cost, or low PSNR with low computational cost. He aims for high PSNR with low cost. In the first stage of his method, a median-type noise detector is used to detect the pixels that are likely to be corrupted by salt-and-pepper noise. In the second stage, the image is denoised by using an edge-preserving statistical jump regression analysis based on the uncorrupted pixels. A number of examples showed that his proposed approach had the ability to obtain better tradeoff between denoising performance and computational complexity.

Task-based information content of medical images
Angel Pineda (California State University)
Dr. Pineda started with a "birds eye view" of the field of task-based assessment of medical image quality. He explained that medical images are typically obtained with a clinical task in mind, and these tasks can often be modeled as signal detection or parameter estimation. He went on to speak about the inadequacies of the signal-to-ratio measure of image quality. In his talk, he defined the

information content of medical images based on the performance of mathematical models for clinical tasks using those images. To quantify this type of information content he defined the task (the intended use of the images), the statistics (the sources of variability in the data), and the observer (how to obtain the information from the images). This task-based optimization was shown to be useful in a wide variety of settings. He went on to present results regarding how higher resolution projections could be used to improve the noise properties of CT reconstructions. He also reported that the effect of binning is object-dependent and lower resolution detectors lead to worse noise in reconstructed images. This measure of information content could also be used to evaluate and optimize methods to reduce the size of large data sets. He concluded with a summary messages, including that the effect of binning is object-dependent and that dimension reduction of the data needs to account for the observer.

Classification and visualization of neural patterns using subspace statistical techniques
Remus Osan (Georgia State University)
Dr. Osan is interested in how the brain achieves real-time encoding of processes. He began by showing how new developments in experimental recording technologies have enabled neuroscientists to record large and complex neural data sets. The improvements in technology have also allowed for a change in the focus of neuroscientists from the single-unit level to the multi-units level. As a result, methods for handling big data are needed in order to investigate temporal and spatial patterns, and also to enable the scientists to have an intuitive understanding of the complex data. In his study, Dr. Osan and his collaborators made use of eigenvalue/eigenvector methods, such as Principal Component Analysis (PCA) and Multiple Discriminant Analysis (MDA) for representing the large-scale data in lower dimensions and for pattern classification. He presented applications of these methods to data from large-scale multi-electrode recordings in the hippocampus and from optical imaging data from the olfactory receptor neurons (ORNs). Dr. Osan then applied these subspace analysis techniques to data containing experimental recordings from neurons of different animals and brain regions, while revealing their usefulness and potential for uncovering neural codes hidden in complex and dynamics population patterns. For the olfactory data sets presented, his methods indicated that different neural codes are present in the olfactory bulb, creating distinct inputs to the local network. The temporal features of the associated population firing rates are in agreement with the behavioral detection times for odor detection in rats. In addition, the cluster structures created by MDA/PCA allowed him to examine the role of sniffing during odor perception. Finally, Dr. Osan presented a potential pitfall: using a data set where the recordings from lobster olfactory neurons decrease as a function of time as the calcium imaging dyes lose their efficiency. In this case, the low-dimensional structure created contained artifacts, and Dr. Osan showed that filtering is needed as a preprocessing step before his methods of analyses could be used.

<u>Current Topic Workshop: Molecular to Systems Physiology</u>
May 5-9, 2014
Organizers: Daniel Beard (University of Michigan), Laura Ellwein (Virginia Commonwealth University), and Mette Olufsen (North Carolina State University)
Reported by: Jae Kyoung Kim, Joshua Chang, Márcio Mourão

MONDAY, MAY 5, 2014

On the mechanisms of sensing unfolded protein in the endoplasmic reticulum
Santiago Schnell (University of Michigan)
Protein folding is assisted through enzyme catalyzed chaperone network in the endoplasmic reticulum (ER). Failure of protein folding causes many diseases in old age, such as diabetes and Huntington disease. A sudden increase in the demand for a protein, or the disruption of a folding reaction, causes an imbalance between protein-folding load and capacity of the ER, which can lead to the accumulation of unfolded protein in the ER lumen. Three model mechanisms have been proposed for how these enzymes sense the unfolded protein load in the ER lumen: (i) direct recognition, (ii) indirect recognition, and (iii) hybrid recognition. Dr. Schnell compared simulation results of mathematical modeling with experimental data to identify the best model protein for prediction of the unfolding response. In particular, he compared simulations from three models with experimental data measuring the relationship mRNA splicing response to system perturbation. From this, he identified that the hybrid model combining parts from each of the three sub-models can reproduce the experimental data correctly.

Molecular Signatures of Cells during Hypoxic Stimulated Tissue Growth
Amina Qutub (Rice University)
Dr. Qutub discussed how to use a computational systems biological approach for understanding the hypoxic response across scales. In order to answer why the structures of blood vessels are different depending on tissues, she used a 3D agent-based angiogenesis model to explore the effect of growth factor on blood vessels. In the process of developing the model, a genetic search algorithm was used. Second, she proposed an algorithm that defines the phenotype of a cell type from the cell image. In this algorithm, a watershed segmentation algorithm was used for the segmentation of cell images, employing 56 metrics with 7 categories, including cell-cell contact, texture, and cell community. Using image processing and clustering analysis, she revealed the phenotype as a function of growth factor. Finally, she discussed how to detect the difference between patients who have a good response to a drug or not by applying machine learning to proteomic cell data.

Discussion: Integrating multiple-scale biophysical processes
Discussion Leader: Daniela Calvetti
In the discussion session, participants discussed key questions in developing multi-scale biophysical processes:

1) How to link in vitro and in vivo data
2) Modularity of models
3) How to handle cell/neuron heterogeneity
4) Variability and uncertainty in modeling and experimental data
5) The importance of good information for parameters
6) How to toggle, that experimentalist do not consider it important to measuring kinetic constants
7) How can we understand complex models

Persistence, Permanence, and Global Stability in Biological Interaction Networks
Gheorghe Craciun (University of Wisconsin)
Biological systems consist of complex biochemical interaction networks. Dr. Craciun discussed how to derive network-based properties using mathematics. In particular, he introduced deficiency theory for the complex balanced system: for a reversible reaction network with deficiency zero, the system has a complex balanced equilibrium, which has a strict Lyapunov function with a minimum at the equilibrium. However, this theorem does not guarantee the system has a global attractor, which is still a conjecture. Dr. Craciun showed that one way to prove this conjecture is to show the complex balanced system is persistent. Finally, he proposed another conjecture: weakly reversible mass action dynamical systems are persistent.

Mathematical modeling of Renal Hemodynamics and Oxygenation: Pathway to Acute Kidney Injury
Anita Layton (Duke University)
Because open-heart surgery needs artificial pumping to compensate for low blood pressure, acute kidney injury can occur. During the process of surgery, various conditions of the body, such as blood flow and body temperature are changed. Dr. Layton discussed the stages of cardiopulmonary bypass (CPB) surgery at which the kidney is most vulnerable to hypoxic injury. Through the mathematical modeling of afferent arteriolar vasomotion, she found that the CPB-rewarming stage is the most vulnerable, since consumption of oxygen is much higher than delivered oxygen.

How Mathematics can Contribute to Genomic Medicine
Michael Reed (Duke University)
Biological systems have mechanisms that maintain the homeostasis of certain conditions, such as body temperature. Dr. Reed showed that we can derive surfaces that show the relationship between genetic polymorphisms and phenotype variables by using mathematical modeling. In particular, he showed how to derive a surface for dopamine level with respect to activity of dopamine transporters (DAT) and tyrosine hydroxylase (TH). Because the loss of dopamine level control leads to Parkinson's disease, it is important to maintain the dopamine level at a certain range. By deriving the surface with mathematical modeling, he showed that dopamine level is still maintained in response to various polymorphisms, but the position of phenotype moves to the edge of surface, where homeostasis is maintained. This study indicates that genomic medicine can propose medical advice tailored to the patient's genotype in order to move the patient back towards the middle of the homeostatic region.

Colloquium: Recent Advances in 3D Blood flow Simulation: From Parameter Estimation Methods to Clinical Applications
Alberto Figueroa (Kings College London)
Dr. Figueroa gave an overview of methods for 3D blood flow modeling. In particular, he focused on efficient and automated parameter estimation techniques. He found that reducing the 3D model to a 1D model provides an efficient and accurate way to estimate the initial parameter set. Then, using Kalman filtering techniques, he estimated the uncertain subset of augmented model states or

model parameters. Interestingly, he noted that the accuracy of the parameter estimation changes significantly depending on the accuracy of the initial guess.

TUESDAY, MAY 6, 2014

A Stochastic Approach to Nonlinear Mixed Effects Modeling
Hien Tran (North Carolina State University)
Noise in biology can present itself in many ways, and the proper handling of this noise is important for both the methodologies and the modeling process. Dr. Tran discussed the advantages of the implementation of stochastic differential equations into a nonlinear-mixed effects modeling framework over the typical ordinary differential equations. For this, he introduced the mixed effects model, which considers both fixed effects for population parameters and random effects incorporating uncertainty associated with inter and intra individual variability. He proposed how to use this approach to analyze pharmacokinetic Metformin clinical data. With this example, he shows that Kalman filter techniques to get the optimal estimation of measurement provide a more accurate stochastic differential equation model.

Multi-scale challenges in brain cellular metabolism
Daniela Calvetti (Case Western University)
The brain is a highly metabolic organ, which consumes more oxygen and glucose than other organs. Dr. Calvetti discussed the challenges and benefits associated with development of multi-scale models for brain cellular metabolism. A lumped metabolic model does not consider the delay in the reaction due to diffusion and translocation, whereas this delay is included in the multi-compartment model. However, most multi-compartment models for the brain usually misses the spatial resolution, such as heterogeneous tissues with different volume size (multi-domain structure). To resolve this issue, she proposed a model with three subdomains (extracellular space/neuron/astrocyte) having multi-domain structure and different diffusivity of metabolites. Furthermore, in the model, the diffusion in the boundary occurs only through capillaries. This detailed and realistic model can reproduce the clear correlation between glucose uptake and lactose production in contrast to the heuristic model.

Recent advances in uncertainty quantification for material parameters in arterial network simulations
Leif Hellevik (Norwegian University of Science and Technology)
Dr. Hellevik presented recent progress in the ongoing development of a framework for the simulation of pressure and flow propagation in arterial networks, focusing on how the effect of uncertainties in model parameters (correlated and uncorrelated) may be quantified. The framework, dubbed Stochastic Arterial Flow Simulations (STARFiSh), employs a number of mathematical techniques and algorithms to derive a sensitivity index for each parameter; and he has found that the sensitivity of pressure changes depending on the organs themselves. The framework flexible, allowing for the incorporation of various organ models and multi-scale models for phenotypes such as arterial compliance.

Discussion: Practical approaches to multi-scale physiology modeling

Discussion Leader: Alberto Figueroa (Kings College London)
In the discussion session, participants discussed challenges and opportunities in practical modeling development:

1) To merge existing models, defining the compartments of system should happen prior to model reduction.
2) Before developing the model, we need to define the purpose of model.
3) From a clinical point of view, simple models seem to be the most practical.
4) Models are helpful for conducting experiments and may be used to move science forward by making problems simpler and improving the understanding of the field.
5) *In silico* clinical trials, assisting diagnosis, and testing the engineered tissue can be important practical outcomes of modeling.
6) The purpose of modeling might be asking the question.

Model Reduction in Biochemical Reaction Networks
Carsten Wiuf (University of Copenhagen)
Dr. Wiuf discussed the problem of model reduction for stochastic and deterministic biochemical reaction networks. He noted that model reduction is important to understand on a purely theoretical basis because it is often performed unintentionally when the reaction network is not fully known. Dr. Wiuf's work has focused on answering several questions of reduced models. These questions include whether one can say anything about a true network from an incomplete model of it, issues of conserved quantities in reduced models, issues of the dynamics about steady states and whether they are conserved in the model reduction procedure, and whether trajectories in reduced models converge to trajectories in the complete model.

Focusing on the procedure of reduction by the elimination of intermediate transient species, Dr. Wiuf addressed many of these questions. He discussed how extension networks, or networks that consist of core reactants and intermediate states, collapse to the core network. By solving the combinatorial problem of summing over the rate constants in the extension network, effective rate constants can be found for the core network where trajectories converge to trajectories in the extension network under certain conditions. Dr Wiuf discussed these conditions and discussed the case of when one should not expect to see convergence.

Modeling Biomedical Systems - An Engineering Approach
Tarun Goswami (Wright State University)
Dr. Goswami presented a variety of real-world problems that his group has solved using mathematical modeling. These problems ranged in scale from the microscopic to the cellular to the tissue level. The approaches to these problems were a combination of statistical and computational, using simple mathematical modeling. For example, he talked about the problem of landmine explosion and understanding the effect that it has on organs and body tissues as well as structures like the neck and the spine. Computational modeling of these injuries relies on material properties of body tissues that are not readily available and need to be culled from other studies. When available, this information uses finite element methods to simulate the stresses and strains in tissue as a result of the injury.

Dr. Goswami also discussed how computational approaches are useful for assessing the effectiveness of medical devices in many contexts. When the devices fail, computational modeling has allowed one to identify the stresses and strains that the device is subject to in order to find weak points. For instance, his group assessed total shoulder replacements and explained the presence of continued dislocations of the humeral head. Finally, computational modeling in his group has shed light on aging and weightlessness with applications to space travel.

Codeword annotation for sharing and merging physiological models: Part 1
John Gennari (University of Washington)
The elephant in the room in mathematical biology is the question of reproducibility. Although the modeling community is relatively small, many existing models for the same phenomena are available. When initiating a new modeling project, the unspoken truth has been that while prior literature is helpful, it is often impossible to re-implement a model directly from a paper without hiring the authors, even in the case where source code for the original model is available. The problem lies in model documentation, as code "in the wild" is often poorly annotated. There is also a general desire to make modeling work more modular, so that different models can be combined together more easily.

In this talk, Dr. Gennari introduced his group's solution to this problem. They have developed a software package called SemGen, which abstracts models from their raw code and can semi-automatically merge different models. SemGen was introduced as a particular piece of the overall solution, but the need for more comprehensive use of model repositories using standardized code-words or terminologies and ontologies is still desirable.

Codeword annotation for sharing and merging physiological models: Part 2
Daniel Cook (University of Washington)
Following Dr. Gennari's introduction to the issues facing modelers and his group's potential solution to the problem, Dr. Cook spoke about the technology behind SemGen and the details of how it works. The idea for SemGen is to make a model description service that is robust enough to handle any of the different process domains found in biophysics. A key to their solution to this problem was the development of what they call "physiomaps," which identify the different components of the model and abstracts them such that model states are distinct from the underlying physical processes. The idea behind this approach is to take code from any model language and abstract the code into language-independent SemSim models using SemGen. SemGen is able to identify overlapping portions of different models by analyzing model structure.

This framework also includes the capability for describing structural knowledge and linking this information to biophysics ontology. Of particular use, data annotation is also integrated as composite annotations are available to link models together with data. Finally, Dr. Cook introduced certain model and anatomical repositories that are useful for referencing information relevant to modeling work, and searching through available models for various biophysical processes.

WEDNESDAY, MAY 7, 2014

Ordinal Response Models for Modeling Longitudinal High-Dimensional Genomic Feature Data

Kellie Archer (Virginia Commonwealth University)

The medical community has developed many patient assessments based on ordinal scales, for instance, the Gleason scale for prognosis of prostate cancer patients. Dr. Archer presented a method for evaluating the results of ordinal response data within a high dimensional statistical model. In particular, this model addressed the situation where the number of predictors is much larger than the number of available data samples. This situation is common in genomics studies, where each gene in a microarray can be considered as a predictor of outcome. In these cases, one also typically sees that the predictors themselves are highly correlated.

The method introduced by Dr. Archer is a forward stepwise method based on adding variables into the model and the correlation between predictors and the residual of a corresponding logistic regression model. This method is able to take into account subject-wise variations using random effects. Her group has applied this method to studying gene expression during inflammation as well as the Marshall Multiple Organ Dysfunction Score.

Arterial Stiffening Provides Sufficient Explanation for Primary Hypertension

Klas Pettersen (Norwegian University of Life Sciences)

Dr. Pettersen presented his work regarding the hypothesis that hypertension is caused by stiffening of arteries resulting in dysregulation of the sympathetic system by baroreceptors. Baroreceptors are sensors for blood pressure activated by strain, located in the arches of the aorta, which stiffens with age. Dr. Pettersen examined this hypothesis in the context of explaining aging related hypertension. His approach involves aggregating several existing models. Using the Smith lumped model for circulation, the Bugenhagen baroreflex model, the Beard composite cardiovascular baroreflex model, and the King model for how the aorta changes with aging, Dr. Pettersen examined how changes of strain in the aorta caused by aging induce changes in the firing rate of the baroreceptor. He found nonlinear changes in the pressure-strain curve in the aorta. His modeling effort ruled out the alternative hypothesis that the pressure regulation is due to the kidneys. Overall, the modeling work supports the view that stiffening of the aorta causes the baroreceptors to misinform the circuit responsible for blood pressure regulation, leading to hypertension. This work suggested that the re-establishment of appropriate baroreceptor responses is a worthy target for therapy.

Assessing vascular risk factors for glaucoma using a mathematical model of blood flow in the retina

Julia Arciero (Indiana University - Purdue University of Indiana)

Glaucoma is typically known as a pressure disease, where pressure in the eye leads to stress in the eye, leading ultimately to blindness. Yet, one third of glaucoma patients have normal eye pressure, so pressure cannot be the only explanation for the development of glaucoma. Dr. Arciero presented work on whether blood flow changes, rather than blood pressure, may be the factor that decides progression to glaucoma. Dr. Arciero used a 3D model of the hemodynamics in the eye to predict when flow through the central retinal artery (CRA) is changed by the deformation of the CRA.

She created this model by coupling a previously developed fluid-structure interaction system model of the CRA to a vascular wall mechanics model.

The model predicted a 14% decrease in retinal perfusion if oxygen demand is decreased by 50%, and a 33% increase in perfusion if demand is increased by 50%. These responses are impaired significantly if the metabolic or carbon dioxide mechanisms of retinal blood flow autoregulation are impaired. Using oximetry maps, she extracted the amount of oxygen consumed by from veins by the eye. This information informed the model by providing a view of oxygen demand. While glaucoma patients have lower oxygen demand, which suggests that oxygen is a secondary effect, glaucoma patients are typically on medication that affects oxygen demand in the eye. Overall, the model results suggest that impaired autoregulation under conditions of elevated metabolic demand, or under decreased mean arterial pressure, may increase the risk of ischemia.

A structured tree model for the pulmonary circulation
Nick Hill (University of Glasgow)
Dr. Hill presented his work on pulmonary circulation using a one dimensional fluid dynamics model where smaller arteries in the system were modeled as a tree. The model took into account the varying resistances and pressures in the system, and was constrained used simple conservation laws and asymmetry rules. Patient-specific geometry using MRI was used in order to parameterize the model, where the ratio between length and diameter of the vessels played a key role. Within the model, many experiments were performed simulating hypertension that resulted from stiffening of the vessels and vascular rarefaction that resulted. The model was able to explain an experimental observation of biphasic patterns in pulmonary vein return flow. He then used the model to examine the differential impacts on hypertension with respect to stiffening of vessels in different levels. The model reproduced simulated results that are in good agreement with clinical observations, showing that even a simple model based on a few physical characteristics of the system has predictive power and may be useful for assisting diagnosis and treatment of lung circulatory diseases.

Personalization of 1D Wave Propagation Models of the Cardiovascular System
Frans van de Vosse (Technische Universiteit Eindhoven)
Dr. van de Vosse presented a one-dimensional model of blood flow wave patterns in arteries. This model was motivated by the desire to express nonlinear behavior of arteries with respect to changes of pressure. He used the model to make predictions for whether particular clinical interventions are effective and worth the risk in particular patients. The predictions were similar to ones made by trained surgeons, and was found to perform slightly better than human surgeons. The model went beyond supplying a single yes/no answer for whether to perform particular interventions, but rather quantified the degree of certainty in a particular decision. This enables the practitioner to balance the potential rewards of the intervention against the risk of potential complications. This uncertainty was based on an estimation of model sensitivity, which in prior literature had been computed using Monte Carlo simulations. Dr. van de Vosse introduced some methods for performing this task based on polynomial chaos expansion that are less computationally extensive.

Image-based 3D quantification and reconstruction of coronary artery morphology in the context of stenting as treatment of cardiovascular disease
Laura Ellwein (Virginia Commonwealth University)
Dr. Ellwein spoke about the extraction of information from images in the context of the inverse problem of determining artery morphology for deciding whether stenting is efficacious. Arterial geometry is a great risk factor when it comes to heart disease. Using patient-specific arterial geometry, fluid dynamics can be used in order to determine blood flow. The first step in this analysis is the extraction of vessels from images. Dr. Ellwein gave an introduction to several commonly used vessel segmentation methods based on either edge or intensity information in images. Statistical analysis was used to compare bifurcations and to look for clustering of particular morphologies with particular health outcomes. The method for extracting patient-specific vascular morphology combines various types of data such as CT and OCT. Statistical analysis of patients before intervention and six months after intervention reveal how vascular morphology relates to the success of the stenting procedure.

Patient-specific parameter estimation in computational hemodynamics: from simulations to assimilations
Alessandro Veneziani (Emory University)
Dr. Veneziani spoke about computational challenges associated with the many inverse problems that arise when studying biology. His group is particularly interested the inverse cardiac conductivity problem, where the goal is to reconstruct patient-specific cardiac conductivities using measurements by inverting the bidomain equation. The common approach to this problem involves the use of gradient minimization schemes such as Broyden-Fletcher-Goldfarb-Shanno BFGS algorithm. The question is how to apply optimization techniques, which are defined over finite parameter sets, to PDE where the elements are continuous. Dr. Veneziani discussed the discretization of the problem and the challenges therein.

Inverse problems are often computationally challenging because one needs to solve the forward problem many times. Dr. Veneziani spoke about efforts by his group on the front of model reduction of the forward problem, in order to reduce the degrees of freedom on the problem. Often the desired solution to a problem is coarse and a sparse basis is sufficient. As he demonstrated, the model given by the first few singular values of a complete model can often capture the behavior desired. This finding is important, since such computational shortcuts are necessary for any reasonable chance at achieving true patient-personalized treatments.

THURSDAY, MAY 8, 2014

Modeling blood pressure and heart rate dynamics in patients with orthostatic intolerance
Mette Olufsen (North Carolina State University)
In this talk, Dr. Olufsen discussed the challenges present in mathematical models of blood pressure and heart rate dynamics in the context of orthostatic intolerance. Young women are more affected by this problem, with symptoms that include lightheadedness and fainting. Because these symptoms are common to many diseases, it is hard to establish a correct diagnosis. The hypothesis is that orthostatic intolerance is the result of an imbalance of blood pressure and flow, as a

consequence of standing upright. In this context, Dr. Olufsen further defined baroreflex regulation, which is a core mechanism that acts to maintain the homeostasis of blood pressure. Using heart rate data from both rats and humans, she discussed ways in which cardiovascular models can be adapted to display patient-specific behavior. In particular, she discussed the addition of respiration mechanisms in the model to mimic experimental data using blood pressure as an input. The heart rate changes over time with different pressures modeled the experimental data well. Dr. Olufsen further discussed how sensitivity analysis on the differential equation model can be used to optimize the model. Using a structured correlation analysis and a global sensitivity matrix, she identified a subset of the parameters that can be correctly estimated given the model and the available data. The talk ended with a major open question, whether one can identify parameters that can be used to describe data at non-equilibrium.

The arterial baroreceptor reflex: a model system for multi scale modeling with clinical significance

John Schild (Indiana University)

Dr. Schild discussed his experimental results on the arterial baroreceptor reflex. He started by discussing the importance of the baroreceptor reflex as a negative feedback for the control of heart rate. He then provided a description of the aortic baroreceptor reflex in the rat, the predominant model for his experimental studies. The population of baroreceptors can be categorized in two groups: myelinated (A-Type) and unmyelinated (C-Type), which are believed to have different sensitivities to blood pressure. Experimental results suggest that myelinated receptors have higher sensitivity to blood pressure and respond to acute changes in arterial blood pressure. The unmyelinated receptors are believed to have higher thresholds or less sensitivity and function towards controlling mean arterial pressure. Dr. Schild then described results in female rats that show a distinct myelinated receptor with a mix of characteristics of the A and the C type (Ah-Type). His main question is: what is the physiological role of Ah-Type aortic baroreceptors identified in females? He hypothesized that these differences may partially explain the enhanced parasympathetic control of blood pressure in females. Other important points include a comparison between the rat and the human and the discussion of a major open question: in terms of heart control, are men and women wired differently?

Patient specific modeling of the endocrine HPA-axis and its relation to depression: Ultradian and circadian oscillations

Johnny Ottesen (Roskilde University Center)

In this talk, Dr. Ottesen discussed a potential relationship between the Hypothalamic-Pituitary-Adrenal-axis (HPA-axis) and depression. The HPA-axis is a major part of the neuroendocrine system that controls reactions to stress and regulates many body processes. He presented an ordinary differential equations compartmental model of the HPA-axis. This model is capable of showing both ultradian oscillations (generated from the hypothalamus) and circadian oscillations (generated by the circadian clock). The model is capable of reproducing experimental hormone concentration data measured in 29 subjects. Dr. Ottesen applied a non-linear mixed effects model (NLME) to estimate the parameters that provide the global minimum. A distinct characteristic of this method is the ability to use distributions to represent the model parameters. He then compared hypocotisolemic, normocortisolemic, and hypercortisolemic groups and found three key

parameters that best describe the three groups of depressed people. These parameters may represent underlying physiological mechanisms related to depression and can potentially be used to build a tool for individual pharmaceutical treatment plans.

Regulation of renal function: building a detailed and coherent mathematical model

Robert Moss (Duke University) Dr. Moss discussed his effort to build a whole-kidney model. He started by describing important aspects of kidney function, such as the regulation of water and sodium excretion. Whole-body homeostasis is quite sensitive to the excretion of salt and water. A failure to conserve water can lead to dehydration and a failure to excrete enough sodium can lead to hypertension. In particular, renal dysfunction greatly increases the risk of cardiovascular disease (CVD). Most mathematical models treat the kidney as a black box or a single homogeneous nephron, which limits the capacity of predicting the consequences of functional changes in the kidney. Hence, there could be great value in building a mathematical/computational model of the kidney. Dr. Moss compared three different results from his model with experimental data from rats. He compared volume excretion with renal perfusion pressure and as with the experimental data, volume excretion increases with renal perfusion pressure. Dr. Moss then presented a more detailed model of the kidney and evaluated the proximal convoluted tubule (PCB) fractional reabsorption as a function of renal perfusion pressure. In an attempt to move from steady state models to dynamic models, he compared results from this model with experimental data showing that osmolarity increases with time in the kidney. His model qualitatively fits the data. Dr. Moss also presented some ideas for future work, such as the possibility adding key mechanisms or embedding his model into larger models, and he mentioned that dynamical experimental data is an essential component of these efforts.

Mechanisms of blood flow regulation and methods of integration into multiscale cardiovascular system models

Brian Carlson (University of Michigan)

In this talk, Dr. Brian Carlson discussed several theoretical models of mechanisms of blood flow regulation. He is particularly interested in understanding the response of a vessel to pressure, also called the myogenic response. Dr. Carlson described a model that fits experimental data available on diameter as a function of pressure. Comparing to his own data, he then explored the VanBavel model to explain the experimental difference in vessel diameter vs. pressure. The experimental data used was obtained from three different rat strains, but it was shown that animals that recruited more collagen at the initial stages have lower responses than animals that recruited less collagen at the initial stages. The solution presented for this problem was to normalize the data by the initial recruitment of collagen. Dr. Carlson then presented and discussed some of the outcomes of the Hai & Murphy model and the Kapela et al model. Hai and Murphy developed a minimum kinetic model for cross-bridge interactions with the thin filament in the smooth muscle. In this model, Ca2+ dependent myosin phosphorylation is the only postulated regulatory mechanism, following many experimental studies that show that arterial smooth cells respond to cytosolic calcium rises to vasoconstrictor stimulation. Kapela's model shows that the phenomena of recruitment and synchronization of Ca2+ oscillations that generate arterial contraction and vasomotion naturally emerges from a model of a population of smooth muscle cells coupled through their gap junctions. Dr. Carlson also discussed results from the Silva et al paper regarding the role of the endothelial

cell function. He showed that in this model, mesenchymal stem cells (MSC) differentiated into smooth muscle cells and endothelial cells, resulting in increased vascularity and improved cardiac function.

Modeling autonomic and metabolic dysfunction in sleep-disordered breathing using PNEUMA
Alison Hu (University of Southern California)
Dr. Hu presented and discussed a tool (PNEUMA) to model autonomic and metabolic dysfunction in sleep-disordered breathing (SDB). PNEUMA is an integrative model of the respiratory, cardiovascular, and sleep state control, and is built with hierarchical spatial and temporal scales. The general model includes a nervous system (controller) affecting a musculoskeletal system, that in turn provides signals to feedback sensors. Dr. Hu described common symptoms of SDB, which include reduction of air flow by 50% (hypopnea) and complete reduction of air flow (apnea). SDB is quite prevalent in obese individuals and likely related to type 2 diabetes, but the causal pathways are largely not known. Dr. Hu made a distinction between central sleep apnea (CSA) and obstructive sleep apnea (OSA). While the former affects the controller or nervous system, the latter affects the muscular system. Dr. Hu further provided several different hypotheses for why sleep apnea shows a high correlation with metabolic syndrome. To address these hypotheses, she then discussed an extension of PNEUMA by incorporating a metabolic component, representing the regulation of glucose, insulin, glucagon and free fatty acids. Comparing model output and experimental data, they found a correlation between OSA and diabetes and how that affects the homeostasis of the system. They also compared normal function versus OSA and found that OSA increases both epinephrine and B cell mass. Future work includes the completion of the feedback loop from the metabolic system to others and model validation/sensitivity analysis. A major challenge is to reconcile temporal and spatial scales.

Stability and identifiability of biological models
Adam Mahdi (North Carolina State University)
Dr. Mahdi's talk was divided into two parts. In the first part, he discussed some alternative and computationally efficient approaches to determine the local stability of a steady state for multi-parameter differential systems. In the second part, he discussed the important issue of identifiability in biological systems. Dr. Mahdi started by highlighting the relationship between physiological modeling and the importance of tools to do the model analysis, including dynamic analysis and identifiability. He then described tools to analyze polynomial differential equations and address questions such as stability and integrability. Focusing on stability, he addressed the problem of computing stability when at least one of the eigenvalues has a zero real part and the rest of the eigenvalues are negative. While traditional methods do not cover this problem, Dr. Mahdi mentioned the Dulac theorem as a way to determine if a fixed point is a focus or a center. He also discussed the Darboux and integrability theories. Dr. Mahdi plans to develop BioAn as a software package to address stability problems. In the second part of his talk, Dr. Mahdi considered a two dimensional system to introduce the question of structural identifiability. He gave two examples: the Burgers and the Lorentz model. Using these examples, he showed that the question of structural identifiability can be reduced to the question of existence of a coefficient map and that the solution can be found using an algebraic matrix.

Understanding the etiology of complex cardiovascular complex system
Daniel Beard (University of Michigan)
Dr. Beard discussed the use of modeling to understand the complexity of the cardiovascular system. He started by providing a history of hypertension starting in the initial stages of the 20th century. These included research on the kidney, nervous system and arteries. He then discussed the law of blood pressure control introduced by Guyton and Coleman. He pointed out that these laws are functionally tautologies - while they cannot be wrong, they do not offer much information. Dr. Beard then proceeded to discuss cardiovascular function and long-term control in blood flow pressure models. In order to test the Guyton-Coleman hypothesis, he compared different models to experimental data. He also discussed hypertension and addressed the fact that hypertension does not necessarily mean renal dysfunction. Dr. Beard then talked about metabolic function and the role of substrates for oxidative phosphorylation. The feedback of these substrates appears to be quite important. Lastly, Dr. Beard discussed the Frank-Starling law of the heart, relating the stroke volume of the heart and the volume of blood filling the heart. His simulations are in agreement with the law, and shows that the stroke volume increases in response to an increase in the volume of blood filling the heart, or end-diastolic volume (EDV). He concluded by proposing that heart failures emerge as a consequence of metabolic changes, hence the need for additional studies of metabolic changes in heart related diseases.

Toward more comprehensive and data-driven mathematical models of the heart and circulations
Naomi Chesler (University of Wisconsin)
In this talk, Dr. Chesler started by discussing recent work on pressure stretch and stress-strain relationships in cardiovascular disease. They were examined to quantify static mechanical behavior. Tests performed on the extralobar pulmonary artery of mice show that wall stress increases exponentially with strain. These suggest that hypertension leads to the stiffness of the pulmonary artery. Dr. Chesler then showed that structural stiffness is frequency-dependent within physiological frequency ranges only in control mice. She presented images of the pulmonary vascular structure obtained with microCT (X-ray microtomography), followed by a discussion of distal vessel distensibility, which appears to be different for men and women. She then proceeded to talk about impedance changes with exercise in pulmonary arterial hypertension (PAH) patients, where she compared arterial stiffness versus disease severity. She also discussed ventricular function, the single beat method for estimation of end-systolic pressure-volume relation, right heart catheterization (RHC), and MRIs in both dogs and mice.

A progressive loss of system flexibility in the microcirculation: the critical contributor to poor organ performance in the metabolic syndrome?
Jefferson Frisbee (West Virginia University)
Dr. Frisbee discussed the progressive loss of system flexibility in the microcirculation. He started by introducing peripheral vascular disease (PVD) as a disease of blood vessels in the peripheral circulation outside the heart. He then proceeded by describing the Obese Zucker Rat (OZR), a popular obese, type 2 diabetes research model. The Zucker rat was used to evaluate PVD by

measuring alterations to vascular reactivity – dilator vs constrictor. Dr. Frisbee continued with the development of PVD in the metabolic syndrome, and described different altered perfusion responses. His results suggest that bulk flow to muscles is not sufficiently constrained to explain the poor performance of the muscle to resist fatigue, and indices such as dilator/constrictor reactivity, vessel wall mechanics, and capillary density are not strong predictors of functional outcomes. They have determined that altered red blood cell distributions at arteriolar bifurcations are increasingly heterogeneous in OZR muscle. He concluded that the increase of spatial heterogeneity at bifurcations is not compensated for via temporal switching, but is exacerbated by blunted temporal activity.

The virtues of virtual experiments in multiscale modelling
Jon Olav Vik (Norwegian University of Life Sciences)
In his talk, Dr. Vik discussed the benefits of virtual experiments in multiscale modeling. He started by describing the role of models in simplifying reality but with a purpose, followed by an explanation of how to specify an experimental protocol. He provided an example of how one can study ion channel behavior in isolation by standardizing, sharing, and reusing models. Dr. Vik advocated for more experimental repositories as well as separating models from experimental protocols. These should be properly annotated in order to facilitate the linking of models to experiments and data. He used the Bondarenko Markov models, representing the molecular structure and function of ion channels, to explain the benefits of virtual experiments. He also used the Bidomain model as a tool to explain how model simplification can be done. Dr. Vik also discussed meta-modeling, functional curation, and real world, automated lab protocols. He further stressed the need of annotation, model/software development and the continuous integration of knowledge. Lastly, he reinforced the need for standards, emphasizing ontology annotation and providing the BioModels database as an example.

Current Topic Workshop: 2014 ICIAM Scientific Workshop
May 15 – 16, 2014
Organizers: Jose Cuminato (Applied Mathematics and Statistics, University of Sao Paulo), Maria J. Esteban (CEREMADE, CNRS & University Paris-Dauphine), Alistair Fitt (Senior Management Team, Oxford Brookes University)**,** Barbara Keyfitz (Department of Mathematics, The Ohio State University)**,** Taketomo Mitsui (Professor Emeritus, Nagoya University)**,** Mario Primicerio (Mathematics, Università degli Studi di Firenze)

The occasion of the annual Board meeting of the International Council for Industrial and Applied Mathematics (ICIAM) provided a confluence of distinguished applied mathematicians from around the world. This workshop provided a forum to exchange ideas, to review recent developments in applied mathematics, and to allow the local community of mathematical scientists to share this international perspective.

The theme of the meeting was broad, reflecting the range of expertise of these scientists.

The workshop was hosted by the Mathematical Biosciences Institute at OSU, with additional funding provided by the Mathematics Research Institute of OSU and by the Institute for Mathematics and its Applications (University of Minnesota).

Full workshop report is pending.

Summer Undergraduate Program
June 2 - August 15, 2014

The goal of this program is to introduce students to exciting new areas of mathematical biology, to involve them in collaborative research with their peers and faculty mentors, and to increase their interest in mathematical biology. The program consisted of three parts - each including a mix of educational and social experiences: a two-week introduction to mathematical biology (June 2-13, 2014); an eight-week individualized research experience as part of a research team at one of the eight participating host institutions; and a week-long Capstone Conference (August 11-15, 2014).

The two-week program was held June 2-13, 2014 and featured tutorial lectures, computer labs, lab tours, and short-term team efforts designed to introduce students to a variety of topics and methods of research in mathematical biology. The lectures were given by several distinguished researchers. Jim Keener kicked off the two-week program with an overview of Mathematical Biology showing how movement and reaction underlying biological processes are modeled with dynamical systems and other mathematical tools. Dennis Pearl led a discussion of estimating evolutionary histories using the tools of statistical phylogenetics. Neuroscience was represented by Janet Best, including providing a tutorial on mathematical neuroscience. Will Ott led a discussion on the stochastic modeling of gene networks. Winfried Just presented an overview of disease dynamics, and Sebastian Kurtek discussed statistical image analysis. The final such presentation was made by Hal Smith on species competition models. Each of these tutorials were accompanied by a computer lab to introduce them to computational aspects of the problems under study - leaving them with strong practice in MatLab, R, and various web applications. The students also participated in short-term team investigations in these various areas. The labs and investigations were led by Dennis Pearl, Winfried Just, MBI visitor Deena Schmidt, and MBI postdocs Lucy Spardy, Joy Zhou, and Leopold Matamba Messi.

During the two-week program, the students toured labs that use quantitative methods in the biological and medical sciences. The first tour was conducted by Pearlly Yan at the Lumina Next Generation Sequencing lab. Next, Joe Travers opened his neuroscience lab to show students the experiments behind some of the computational and differential equations modeling seen in the program's tutorials. Meg Daly gave the group a tour of Ohio State's Museum of Biological Diversity with its major acarology, plant, insect, fish, and mollusk collections that are available for both teaching and research. The students then toured Libby Marschall's aquatic ecology laboratory where her team of graduate students showed off their work in studies of fish populations in Lake Erie. The final tour of the two-week program was conducted by Lynn McReady, who provided the group with a hiking tour through the living laboratory of the Olentangy River Wetland Research Park and their projects in ecological engineering.

For the 16 MBI supported students, the end of the two-week program marked the start of their summer-long projects at one of the host institutions. This part of the program was held June 16-August 8, 2014 and the host institutions included projects at Arizona State University supervised by Yang Kuang, Fabio Milner, and Rosie Renaut; at the University of Notre Dame supervised by Alexandra (Sasha) Jilkine; at Howard University supervised by Talitha Washington, Mark Burke, Georges Hadded, and Kevin Jones; at Indiana University-Purdue University Indianapolis supervised by Julia Arciero and Yaroslav Molkov; at University of Pittsburgh supervised by Brent Doiron; at the Ohio State University supervised by Sebastian Kurtek and Shili Lin; and at the Virginia Biomathematics Institute at Virginia Tech supervised by Josep Bassaganya-Riera and Hehuang (David) Xie.

The Summer Undergraduate Program ended with a weeklong Capstone Conference which was held August 11-15, 2014. It celebrated all of the nationwide efforts of undergraduate researchers in the mathematical biosciences – not just those of the MBI sponsored REU students. This student-centered conference featured a graduate studies recruitment fair for Institute Partner Schools; panel discussions on career and graduate opportunities in mathematical biology; keynote talks from prominent mathematical bioscientists geared toward student interests; an opening reception and a mid-week social event at the Columbus Zoo & Aquarium followed by a dim sum banquet dinner. Most importantly, the capstone conference offered undergraduate students doing research projects in the mathematical biosciences an opportunity to present their work on the national stage. This included 24 half-hour oral presentations and 30 poster presentations on individual and team projects. This next generation of mathematical biologists were all actively engaged in the lively discussions around each topic and made the conference a terrific success.

MBI thanks all of the Institute Partners who opened their campuses to serve as hosts for these talented undergraduates and their institutional representatives who also served as the organizing committee for the entire summer program.

MBI-NIMBioS-CAMBAM Summer Graduate Program
July 7-18, 2014
Organizers: Daniel Forger (Mathematics, University of Michigan) and Paul Francois (Department of Physics, McGill University)
Reported by: Laura Kubatko

A total of 40 graduate students from mathematics and biology participated in the workshop. The topics discussed included a variety of settings in which mathematical models of natural rhythms are used, including applications to ecology, circadian rhythms, sleep, cardiac and neuronal processes, and the cell cycle.

The workshop began with three days of introductory tutorials and computer labs by Danny Forger (University of Michigan) to introduce students to the main concepts involved in mathematical modeling of rhythms and oscillations. The rest of the program featured researchers from the

mathematical and biological sciences who each presented an introduction to theory and applications in a particular area through lecture and hands-on analysis and simulation activities. During the two-week program, the students formed small groups (4-6 students) tasked with preparing a short document reviewing mathematical progress in a particular field discussed during the lectures. Four MBI postdoctoral associates assisted the students with the preparation of these reviews, as well as with the hands-on activities that were coupled with each lecture. The reviews prepared by the groups were presented during the final day of the workshop to the entire set of workshop participants.

The lecturers and their topics were:

- Nancy Kopell (Boston University), Neuronal Rhythms
- Marty Golubitsky (MBI, OSU), Synchrony and Symmetry
- William Schwartz (University of Massachusetts Medical School), Circadian Rhythm
- David Paydarfar (University of Massachusetts Medical School), Respiratory Oscillations
- John Tyson (Virginia Tech), Cell Cycle
- Paul Francois (McGill University), Rhythms in Embryogenesis
- Arthur Sherman (NIH), Glycolytic and Metabolic Oscillations
- Victoria Booth (University of Michigan), Rhythms in Sleep
- Fred Guichard (McGill University), Ecological Rhythms
- Xiaopeng Zhao (University of Tennessee, Knoxville), Circadian Rhythms

The postdoctoral assistants were:

- Jae Kim
- Kang-Ling Liao
- Michael Schwemmer
- Lucy Spardy

F. COMMUNITY INVOLVEMENT IN MBI PROGRAMS

The Director and Associate Directors were in continuous contact with the mathematical and bioscience communities in order to identify areas of opportunity in the mathematical biosciences. To insure that MBI programs have a sustained strong impact, the Director and Associate Directors continue to identify areas for industrial and government participation. They have started to build a stronger Institute Partner Program and they are working to develop corporate relationships while strengthening the sponsored postdoctoral program.

Sponsored Postdoctoral Fellows

MBI expects to have a portion of its postdocs sponsored by a company, institute, or bioscience department. Each sponsor pays a percentage of the postdoc's compensation, benefits and overhead, and in return, gets an equal percentage of time and effort from the postdoc. The sponsored postdocs are appointed for one to three year periods. In 2013-2014, MBI had one sponsored postdoc: Michal Seweryn, who began his term in 2012, was cosponsored by the OSU College of Public Health. In 2012-2013, MBI had four sponsored postdocs: Duan Chen, who began his term at MBI in 2011, was cosponsored by Michigan State; Paul Hurtado, who began his term at MBI in 2011, was

cosponsored by the OSU Department of Evolution, Ecology and Organismal Biology; Jincheol Park, who began his term in 2012, was cosponsored by the OSU Department of Statistics; and Michal Seweryn, who began his term in 2012, was cosponsored by the OSU College of Public Health.

Institute Partners

MBI welcomes the participation of other academic institutions in the MBI Institute Partner (IP) Program. The goals of the IP program are to help enable researchers from partner institutions to participate in MBI programs and to increase the national and international impact of MBI programs while encouraging scientific activity and the growth of mathematical biosciences at partner institutions.

IPs are universities, government labs and companies. Typically, a single department (but sometimes a group of departments) enters into an agreement with MBI to become an IP. The IP designates a contact person who is charged with making decisions on behalf of the IP.

The IP program uses MBI matching funds to subsidize the travel expenses of IP member researchers to allow their participation in MBI programs. In addition, each year MBI provides up to $15,000 to support conferences in mathematical biology held at IP institutions. IP representatives are invited to annual meetings to explore research and educational opportunities and provide input for future institute programs. IP members also receive MBI newsletters, proceedings, and annual reports.

2013-2014 Institute Partners

1. Arizona State University
2. Battelle
3. Boston University
4. Case Western Reserve University
5. Cornell University
6. Drexel University
7. Duke University
8. Florida State University
9. Howard University
10. IBM
11. Indiana University-Purdue University Indianapolis
12. Instituto Gulbenkian de Ciencia, Portugal
13. Iowa State University
14. Konkuk University, South Korea (New IP in 2013-2014)
15. McGill University, Canada
16. Michigan State University
17. Mississippi State University
18. Mount Sinai School of Medicine (New IP in 2013-2014)
19. National Tsing Hua University, Taiwan
20. New Jersey Institute of Technology

21. The Ohio State University
22. Ohio University
23. Penn State University
24. Princeton University
25. Texas Tech University
26. Trinity University
27. Tulane University
28. University of Bath, United Kingdom (New IP in 2013-2014)
29. University of California at Davis
30. University of California at Irvine
31. University California at Los Angeles (New IP in 2013-2014)
32. University of California at San Diego
33. University of Cincinnati
34. University of Exeter, United Kingdom
35. University of Georgia
36. University of Glasgow, Scotland (New IP in 2013-2014)
37. University of Houston
38. University of Iowa
39. University of KwaZulu-Natal, South Africa
40. University of Maryland (New IP in 2013-2014)
41. University of Maryland at Baltimore County
42. University of Miami
43. University of Michigan
44. University of Minnesota
45. Universidad Nacional Autónoma de México, Mexico
46. University of Notre Dame
47. University of Nottingham – CMMB, United Kingdom
48. University of Oxford, United Kingdom
49. University of Pittsburgh
50. University of Southern California
51. University of Twente, Netherlands (New IP in 2013-2014)
52. University of Utah
53. University of Washington
54. University of Waterloo, Canada
55. University of Wyoming
56. Vanderbilt University
57. Virginia Tech

Worshops at Institute Partners

MBI helped support four workshops held at MBI partner institutions in 2013-2014:

1. University of Pittsburgh, March 10-12, 2014: Travel Grant for young researchers to attend "Nonlinear Dynamics and Stochastic Methods: from Neuroscience toOther Biological Applications. In honor of G. Bard Ermentrout's 60th Birthday"

2. Texas Tech University, October 4-6, 2013: Travel Grant for young researchers to attend "The Fourth International Conference on Mathematical Modeling and Analysis of Populations in Biological Systems" (ICMA IV)
3. Virginia Bioinformatics Institute, August 14-16, 2013: "International Conference on Computational Cell Biology: From the Past to the Future"
4. Arizona State University, June 10-13, 2013: Travel Grant for young researchers to attend the SMB Annual Meeting

Corporate Involvement
As an extension of the IP program, MBI is working to develop corporate relationships among pharmaceutical and bioengineering companies. The goal of corporate involvement is to identify areas where mathematical sciences can be helpful to nonacademic businesses. In building corporate involvement, companies are invited to present industrial challenges and problems to MBI audiences and to participate in MBI programs and workshops. Discussions are currently in progress to expand MBI's corporate interactions which include a postdoc visitation program and mentoring opportunities with corporate partners. Current nonacademic IP members include Battelle and IBM. In the past, MBI had corporate partnerships with Eli Lilly Company, GlaxoSmithKline, Legacy Good Samaritan Hospital, and Pfizer, Inc.

G. DIVERSITY EFFORTS

The MBI diversity mission is to help shape the mathematical biology community in a way that represents the diversity of our society. Enhancing representation will ensure that the Math Biology community benefits from a diversity of ideas, research approaches, and educational strategies. Historically, women, African-Americans, Hispanics, Native American, and Alaskan Natives have been underrepresented in the mathematical biology community, and our efforts target individuals from this group. MBI works at two levels:

- It is MBI policy that each of its programs should actively seek diversity among its participants in gender and ethnicity.
- MBI will sponsor activities that promote mathematical biology and its opportunities in the academic community and will do so in ways that reach the broadest number and types of individuals.

To be most effective, these activities should reach early career students including undergraduates and contribute to increasing the diversity of future mathematical biologists.

Diversity Committee
The Diversity Committee provides consultation and ideas, and helps MBI to carry out its diversity mission.

Current members of the Diversity Committee are:
1. Erika Camacho (Arizona State – Glendale)

2. Ricardo Cortez (Tulane)
3. Helen Chamberlin (Ohio State, ex officio)
4. Holly Gaff (Old Dominion)
5. Maeve McCarthy (Murray State)
6. Kim Weems (NC State)
7. Aziz Yakubu (Howard)

Former members are:

1. Carlos Castillo-Chavez (Arizona State)
2. Joan Herbers (Ohio State)
3. Trachette Jackson (Michigan)
4. Yi Li (Iowa)

Visiting Lecturer Program

The MBI Visiting Lecturer Program 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 consider careers in the mathematical biosciences. In addition to delivering a lecture on mathematical biology that is accessible to an undergraduate audience, the lecturers meet with individual students and with groups of interested faculty and students to further this purpose. There have been eight lectures in the three and a half years that the program has existed. The 2013-2014 lecturers are listed in Section A2.

MBI Conference Awards

MBI has started a new diversity program whereby MBI offers full travel support to winners of a presentation award at conferences that serve minority communities. MBI has presented 14 conference awards in the past two years and the 2013-2014 recipients are listed in Sections A2 and A4. The math institutes have also started their own conference award program modeled on the MBI program.

Participation of Women in MBI Programs

Several years ago the MBI Board of Trustees decided that women should constitute at least 20% of invited participants and 20% of speakers at all MBI meetings. Organizing committees have responded well to this guideline. During MBI's first eight years the percentage of female speakers was 14.7% and, so far, during the current grant that number is 24.4%, an uptick of nearly 10 percentage points. The corresponding numbers for female organizers are 16.5% and 22.8%. It should be noted that the total percentages of female attendees only rose from 27.3% to 27.6%. Data tables are listed in Section A3.

During the current grant period MBI has supported or hired 46 Postdoctoral Fellows. Of these 19 (or 41.3%) are women. Likewise, MBI has hired one African American and three Hispanic postdoctoral fellows (or 8.7% underrepresented minorities).

MBI Capstone Conference Awards (beginning in 2014)

The Capstone Conference Awards are modeled on the MBI Conference Awards, and are made to underrepresented minority students nominated by their mentors. The award enables the participation of recipients in the MBI REU Capstone Conference and includes reimbursement of travel expenses (round-trip economy class airfare, ground transportation, etc), and direct-billed accommodations. The MBI Diversity Committee selects three winners each year.

2014 Capstone Conference Award recipients:

1. Dominic G. Gray, Norfolk State University
2. Kennedy Agwamba, Harvey Mudd College
3. Jamal E. Moss, North Carolina State University

MBI Visiting Scholars

MBI has had an active visiting scholars program mainly for advanced students from our institute partners of Howard University and KwaZulu Natal. Visiting Scholars in 2013-2014:

Faculty

1. Edward Lungu, University of Botswana, May-Aug 2013
2. Abdul-Aziz Yakubu, Mathematics, Howard University, July 2013
3. Najat Ziyadi, Mathematics, Howard University, July 2013
4. Farai Nyabadza, Mathematics, University of Stellenbosch, April – June 2014

Students

1. Patrick Phepa, Mathematics, Statistics and Computer Science, University of KwaZulu-Natal, April 2014
2. Komi Afassinou, School of Mathematics, Statistics and Computer Science, University of KwaZulu-Natal, August 2013 - September 2013
3. Obiora Collins, School of Mathematics, Statistics and Computer Science, University of KwaZulu-Natal, August 2013 - September 2013
4. Eddy Kimba Phongi, School of Mathematics, Computer science and Statistic, University of KwaZulu-Natal, August 2013 - September 2013
5. Nourridine Siewe, Mathematics, Howard University, July 2013 and January 2014

Math Institutes Diversity Programs

The MBI is actively involved in the Mathematical Sciences Institutes Diversity Committee, which includes participants from all NSF supported math institutes. A major aim of the committee is the development, organization and sponsorship of national events and programs that foster diversity in the mathematical sciences, and build community. We have worked with other Math Institute Diversity committee members to obtain support for events and fellowships in support of underrepresented minorities.

MBI representatives participate in conferences and workshops sponsored by the Math Institutes Diversity Committee and its collaborators. Examples of involvement include:

- MBI representatives (Postdocs and Associate Director) attend the annual *Modern Math Workshop* to provide scientific talks and to advertise MBI programs
- MBI representatives attend *SACNAS*, to serve as poster judges, mentors to early career trainees and to coordinate the Math Institutes Booth

- MBI postdocs attend the *Field of Dreams* conference, to offer scientific talks and to mentor early-career trainees

H. EVALUATION OF MBI PROGRAMS

MBI formally evaluates its programs in two ways. First, starting in 2010 with funding from the current grant, MBI has had a contract with Strategic Research Group (SRG, http://www.strategicresearchgroup.com/) to perform an independent evaluation of MBI programming based on online questionnaires and personal interviews. Second, every 2-3 years, MBI sends e-mails to former participants and visitors to collect specific information on outcomes from their respective visits, including collaborations, papers written or significantly influenced, and many others. Informally, MBI staff and directors are listening and watching for information that can improve MBI programs, and many improvements have been made this way.

The evaluation process with SRG
SRG independently conducts the evaluation of MBI programming. Evaluation begins with SRG Partner/Principal Investigator Kathleen Carr meeting with Golubitsky and Nance to discuss scope and goals. SRG then designs and implements the evaluation instruments, collects and houses the resulting data, performs in-house analysis, and issues reports to MBI.

SRG meets three to four times a year with MBI Directors to discuss results. SRG's general expertise provides MBI with both the information and analysis that influence MBI programming, and does so in a way that MBI would not be able to do on its own.

How working with SRG has helped MBI
MBI has made adjustments based on SRG reports and information and MBI has also learned what it is doing well that should not be changed. This has happened on levels ranging from the big picture (postdoctoral mentoring; the attitudes and involvement of bioscientists) to the small (afternoon snacks and better coffee at events). Here are some ways in which
SRG evaluations have helped change MBI programs.

Post-doc program

- Influenced changes to the post-doc career ("professional") mentoring program
- Influenced changes and clarifications to post-doc scientific mentoring
- Led to clarification of post-doc teaching opportunities

Biosciences participants

- We learned that our bio-based visitors were often hesitant about coming to a math institute. We are now asking our workshop organizers to take this into account in their programming.
- MBI is starting to ask workshop organizers to create tutorials aimed at participants from the biosciences that will be on the web before the workshops

Logistics

- Tentative schedules are now online earlier
- Use social media better
- Consider shorter workshops
- Pointed out inadequacies in MBI online registration, which are being addressed

REU & Capstone Conference

- We changed and improved logistics of this complex program, including our internal funding model, handling of travel for the students, and the logistics for the Capstone Conference.

Positive reinforcement: workshop participants like

- The extra discussion time in our workshop schedules
- The diverse communities that speak and participate
- The number of participants
- The logistics, support, and general staff interaction

Moving forward with SRG

In the new grant, SRG will continue evaluating MBI programs (workshops, post-docs, long-term visitors, and Capstone Conference). In addition, MBI expects to work with SRG to learn more about the long-term impact of MBI programs, and to better evaluate the Institute Partner program and MBI web initiatives. Also, locally, Nance will write a formal summary for each of the reports received from SRG.

Annual Report for DMS-0931642
For Year 2014-2015

Included, as an appendix, in this report is the 2013-2014 MBI Annual Report.

Summary of MBI Programs in Academic Year 2014-2015

The MBI emphasis program for the 2014-2015 year was on *Cancer and its Environment*. The Organizing Committee was: Alexander (Sandy) Anderson (Integrated Mathematical Oncology, H.Lee Moffitt Cancer Center & Research Institute), Rick Durrett (Mathematics, Duke University), Mariam Eljanne (Physical Sciences-Oncology, NIH), Avner Friedman (Mathematics, Ohio State University), Kirk Jordan (Data Centric Systems, IBM Corporation), John Lowengrub (Mathematics, University of California, Irvine), Guido Marcucci (Comprehensive Cancer Center, Ohio State University), Hans Othmer (School of Mathematics, University of Minnesota), and Vito Quaranta (Vanderbilt Ingram Cancer Biology Center, Vanderbilt University).

Cancer is one of the world's biggest killers. Cancer is initiated from cells with specific genetic mutations that cause them to lose control of proliferation. This loss of proliferative control, whilst necessary, is not sufficient to cause cancer; subsequent mutations and selection need to occur. Cancer is an evolutionary disease, where rounds of mutation and selection will drive the emergence of a tumor. The selection pressures that a growing tumor encounters are manifold but can largely be classified as microenvironmental. The tumor microenvironment consists of the extracellular matrix, growth promoting and inhibiting factors, nutrients (including oxygen and glucose), chemokines, and importantly, other cell types including (but not limited to) fibroblasts, immune cells, endothelial cells and normal epithelial cells. In order for selection to operate properly there needs to be variation in the tumor population -- tumors are known to be genetically extremely heterogeneous. This genetic heterogeneity produces phenotypic heterogeneity in which individual tumor cells can have distinct phenotypic behaviors within the same tumor.

As the tumor mass grows, so does the heterogeneity; eventually the mass becomes too large to be supported by nutrient diffusion alone, so some subset of the tumor population then becomes hypoxic. This hypoxia will eventually give way to cell death if nutrient levels continue to fall but the tumor has two ways to combat this problem. First it can begin to utilize a different nutrient source (e.g. glucose) by altering its metabolism and second it can initiate the process of angiogenesis from nearby vessels. The process of recruiting and growing a new vasculature, once fully realized, gives the tumor an almost limitless nutrient source and also a highway to other parts of the human body. Metastases are cells that successfully break away from the primary tumor and initiate new tumors at secondary sites. There can be many of these metastatic cancers at many different sites in the body and ultimately, for most patients, it is these cancers that cause death.

There are hundreds of types of cancer, classified by the tissue from which they arise and by the type of cells involved. For example, leukemia is a cancer of white blood cells, carcinoma is a cancer originating from epithelial cells and glioma is cancer of the brain. There are also many ways

to treat cancer, most of which start with surgery and end with chemotherapy and/or radiotherapy. In recent years we have seen the emergence of immunotherapies and molecularly targeted therapies. Immunotherapies exploit the immune system by either enriching or aiding its ability to attack the cancer. Molecularly targeted therapies exploit the fact that specific mutations are present in a large proportion of the cancer cells and block the activity of these mutations. Both of these new therapies have had differing degrees of success but, as in most treatments, failure is ultimately caused by the emergence of a resistant tumor population that tends to be more aggressive and less easy to treat.

This brief overview illustrates the complex interactions at the molecular, cellular and tissue levels involved in the emergence and development of cancer, and emphasizes the need for mathematical models that synthesize a framework for understanding the existing phenomena and that make testable predictions as to how interventions will influence the outcome.

Autumn 2014 Emphasis Semester Workshops

1. Workshop 1: Ecology and Evolution of Cancer (September 15-19, 2014)
2. Workshop 2: Metastasis and Angiogenesis (October 13-17, 2014)
3. Workshop 3: Cancer and the Immune System (November 17-21, 2014)
4. Workshop 4: Tumor Heterogeneity and the Microenvironment (February 2-6, 2015)
5. Workshop 5: Treatment, Clinical Trials, Resistance (February 16-20, 2015)
6. Workshop 6: Targeting Cancer Cell Proliferation and Metabolism Networks (March 23-27, 2015)
7. Workshop 7: Stem Cells, Development, and Cancer (April 13-17, 2015)

Current Topic Workshops

1. 2014 Workshop for Young Researchers in Mathematical Biology (August 25-28, 2014)
2. Boot Camp: How to Simulate and Analyze Your Cancer Models with COPASI (September 29 – October 1, 2014)
3. Axonal Transport and Neuronal Mechanics (November 3-7, 2014)
4. Evolutionary Game Theory (April 27 – May 1, 2015)

Educational Programs

Joint 2015 MBI-NIMBioS-CAMBAM Summer Graduate Workshop on Nonlinear Dynamics in Biological Systems (hosted at CAMBAM/McGill University) (June 1-12, 2015)

Quantitative bioscience is the application of mathematics, physics and numerical computations to all spheres of biology. It provides a common currency to the understanding of life at the microscopic and macroscopic level, from single molecules to complex ecosystems. It underlies the development of personalized biomedical devices, optimized drug delivery to patients and the prediction of ecosystem health in changing environments. While these challenges are typically addressed within each research area, the required quantitative (mathematical, physical and computational) tools are shared across all areas. The rich stream of experimental data has made it possible for bioscientists to build testable and predictive models that are based on sound data. It is these models, accompanied by statistical and computational approaches that have provided a

patform for experimentalists to undertand the dynamics of their respective biological systems and to guide new experiments. As a result, the field of mathematical and computational modeling has been felt strongly across the biological sciences, including neuroscience, cancer biology, immunology, epidemiology, ecology, and evolutionary biology.

In this summer school, we aim to provide a new generation of trainees with the opportunity to learn more about the basics of this field and give them an overview of the latest advancements made in quantitative biosciences.

Undergraduate Program (June 8 - August 14, 2015)
The innovative program for 15 fully supported students will consist of three parts:

1. One-week program (June 8-12, 2014): Tutorials, computer labs, and short-term team efforts designed to introduce students to a variety of topics in mathematical biology.
2. REU Program (June 15 – August 7, 2015): An 8 week 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, The Ohio State University, Penn State University, University of Pittsburgh, and the Virginia Bioinformatics Institute at Virginia Tech.
3. Capstone Conference (August 10-14, 2015): A student centered conference featuring talks and posters by students doing research in mathematical biology, keynotes by prominent mathematical biologists, a graduate studies recruitment fair, and other special features.

Spatially-varying Stochastic Differential Equations with Applications to the Biological Sciences (July 6-10, 2015)
In biology, ecology, and public health there has been a growth in the use of stochastic differential equations (SDEs) to model scientific phenomena over time. SDEs have the ability to simultaneously capture he known deterministic dynamics of the variable of interest (e.g., chemical levels within a cell, the chemical or physical characteristics of a river, the presence, absence and spread of a disease), while enabling a modeler to capture the unknown dynamics or measurement processes in a stochastic setting.

In this four-day workshop, participants will learn about the use of SDEs to model physical phenomena in the biological sciences. Students will learn how to define and manipulate SDEs, and will understand the difficulties in performing statistical inference on the parameters of SDEs using data. They will relate the modeling of SDEs to the theory of spatial and temporal data analysis, and will carry out a small group project to discover and investigate how to model data from various disciplines within the biological sciences.

The lectures will be taught by a selection of external and internal speakers, each of which have a different experience in different aspects of modeling using SDEs, as well as in spatial and temporal data analysis. Students will learn the material through practical exercises.

Students should come to the workshop with two years of graduate experience in Statistics or equivalent. They should be comfortable with statistical models and theory, likelihood inference,

and have some exposure to Monte Carlo techniques. Students should have taken a course in linear models, and have knowledge of the statistical software package called R (http://www.r-project.org). Some exposure to time series analysis and spatial statistics is helpful, but not essential. Students should bring a laptop to the workshop, preloaded with R. Online material (including videos and exercises) useful for this course will be made available at least a week before the workshop begins.

Postdoctoral Fellows

MBI Postdoctoral Fellow Hires to start in Autumn 2015

1. Farrah Sadre-Marandi (Mathematics, Colorado State University)
2. Reginald McGee (Mathematics, Purdue) - co-sponsored with Kevin Coombes of Biomedical Informatics at Ohio State University
3. Min Wang (Mathematics and Statistics, Iowa State University) - co-sponsored with Kevin Coombes of Biomedical Informatics at Ohio State University
4. Casper Woroszylo (Statistics, Rice University) - co-sponsored with Peter Shields of the Comprehensive Cancer Center at Ohio State University

Post-doc Professional Development Seminar: This monthly meeting is led by Mike Reed and Tony Nance to practice talks of all kinds, discuss career-related issues, and give general guidance to post-docs as they prepare for the next steps in their careers.

External Evaluation of MBI

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

Early Career Award Visitors in 2014-2015

1. Alexandra (Sasha) Jilkine, Applied and Computational Mathematics and Statistics, University of Notre Dame, August 24, 2014 – November 25, 2014
2. Min Tang, Institute of Natural Sciences, Shanghai Jiaotong University, September 1-October 21, 2014 and January 25 – March 2, 2015
3. Harsh Jain, Mathematics, Florida State University, January 1 – April 30, 2015
4. Kun Zhao, Mathematics, Tulane University, January 10 – May 10, 2015

Long Term Visitors in 2014-2015

1. Dan Bates, Mathematics, Colorado State University, August 1 – December 19, 2015
2. Jasmine Foo, School of Mathematics, University of Minnesota, September 1 – October 10, 2015
3. Kevin Leder, Industrial and System Engineering, University of Minnesota, September 1 – October 10, 2015
4. Thomas Hillen, Mathematical and Statistical Sciences, University of Alberta, September 14 – Novembr 23, 2015
5. Rick Durrett, Mathematics, Duke University, September 15 – October 20, 2015
6. Kate Petersen, Mathematics, Florida State University, January 1 – April 30, 2015

7. Ernie Barany, Mathematical Sciences, New Mexico State University, January 12 – May 2, 2015
8. Preethi Gunaratne, Physics, University of Houston, March 1 – April 1, 2015
9. Gemunu Gunaratne, Biology and Biochemistry, University of Houston, March 1 – April 1, 2015
10. Vlastimil Krivan, Biology Center, Czech Academy of Sciences (AVv CR), April 20 – May 22, 2015

Short Term Visitors in 2013-2014

1. Kenny Salau, Mathematics, University of Arizona, August 11-15, 2014
2. Ian Stewart, Mathematics, University of Warwick, September 8-22, 2014
3. James Sneyd, Mathematics, University of Auckland, November 1-4, 2014
4. Bei Hu, Applied and Computational Mathematics and Statistics, University of Notre Dame, October 13-27, 2014 and February 16-27, 2015
5. Mason Porter, Mathematical Institute, University of Oxford, November 9-13, 2014
6. Nourridine Siewe, Mathematics, Howard University, December 12-23, 2014

Long Term Visitor Seminar

With the number and scientific breadth of Long Term Visitors seen above, MBI added a 3rd seminar series during non-workshop weeks featuring talks by MBI Long Term Visitors.

New MBI Institute Partners in 2014-2015

1. H. Lee Moffitt Cancer Center & Research Institute
2. Rutgers University at Camden
3. Rutgers University at New Brunswick
4. Daegu University (South Korea)
5. University of Alberta
6. Virginia Commonwealth University

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.

Public Lecture series

MBI continued to be instrumental in the Science Sundays Public Lecture Series at OSU, including providing lectures by Margot Gerritson, James Sneyd, and Joel Cohen. Science Sundays lectures are held monthly during the academic year 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. A complete listing of the Science Sundays Public Lecture Series can be found at http://artsandsciences.osu.edu/science-sundays.

Visiting Lecturer Program

The Visiting Lecturer Program 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/

Workshops at IPs

From August 2014 – July 2015, MBI helped support two workshops held at MBI partner institutions.

1. **University of Glasgow**, June 10-12, 2015: Travel Grant for young researchers to attend "Glasgow 2nd Workshop on Soft Tissue Modelling"
2. **Ohio State University**, May 24-27, 2015: Travel Grant for young researchers to attend "Workshop on Topics in Applied Dynamical Systems: Equivariance and Beyond"

New Members of MBI Committees

Board of Trustees

1. Carolyn Cho, Quantitative Pharmacology & Pharmacometrics, Merck, Sharp & Dohme (2015 – 2017)
2. Tom Kurtz, Departments of Mathematics and Statistics, University of Wisconsin (2015-2017)

Scientific Advisory Committee

No new members were appointed to start on January 1, 2015. All existing members agreed to continue to serve on this committee.

Diversity Initiatives

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 this year, including SACNAS Modern Math Meeting and AWM. Award winners can be seen at http://mbi.osu.edu/about/diversity-statement/conference-award-winners/ .

Program Initiatives

2015-2016 Emphasis Programs

The theme for the **Autumn 2015** emphasis semester is *Mathematical Molecular Biosciences*.

This one-semester program will bring 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.

An important trend in contemporary life sciences is that with the availability of modern biotechnologies, traditional disciplines, such as physiology, plant biology, neuroscience etc, are

undergoing a fundamental transition from macroscopic phenomenological ones into molecular based biosciences. In parallel with this development, a major feature of life sciences in the 21st century is their transformation from phenomenological and descriptive disciplines to quantitative and predictive ones. Revolutionary opportunities have emerged for mathematically driven advances in biological research. 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 in the past few decades. 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 are 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 is 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 will act as a catalyst to fully exploit these synergies, and create a network of collaborations that will sustain future activities in this area beyond the duration of this program.

Organizing Committee

- Emil Alexov, Computational Biophysics and Bioinformatics, Clemson University
- Ridgway Scott, Computer Science and Mathematics, University of Chicago
- Reidun Twarock, University of York
- Guowei Wei, Michigan State University

The theme for the **Spring 2016** emphasis semester is *Dynamics of Biologically Inspired Networks.*

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.

Organizing Committee

- Peter Ashwin, Mathematical and Physical Sciences, University of Exeter
- Nina Fefferman, Ecology, Evolution and Natural Resources, Rutgers University
- Martin Feinberg, Chemical Engineering & Mathematics, Ohio State University
- Leon Glass, Physiology, McGill University
- Adilson Motter, Physics, Northwestern University
- Mason Porter, Mathematical Institute, University of Oxford
- Ruth Williams, Mathematics, University of California, San Diego

Events 2015-16
Autumn Semester 2015

12. Workshop 1: Geometric and Topological Modeling of Biomolecules (September 28 – October 2, 2015)
13. Workshop 2: Multiple Faces of Biomolecular Electrostatics (October 12-16, 2015)
14. CTW: Uncertainty, Sensitivity, and Predictability in Ecology: Mathematical Challenges and Ecological Applications (October 26-30, 2015)
15. Workshop 3: Modeling and Computation of Transmembrane Transport (November 16-20, 2015)
16. Workshop 4: Mathematical Challenges in Drug and Protein Design (December 7-11, 2015)

Spring Semester 2016

17. Workshop 1: Dynamics in Networks with Special Properties (January 25-29, 2016)
18. CTW: Modeling and Inference from Single Molecule to Cells (February 8-12, 2016)
19. Workshop 2: The Interplay of Stochastic and Deterministic Dynamics in Networks (February 22-26, 2016)
20. Workshop 3: Generalized Network Structures and Dynamics (March 21-25, 2016)
21. Workshop 4: Control and Observability of Network Dynamics (April 11-15, 2016)