

Stochastics in Biological Systems 2011-2012



Mathematical Biosciences Institute



MBI receives major funding from the National Science Foundation Division of Mathematical Sciences and is supported by The Ohio State University. Mathematical Biosciences Institute adheres to the AA/EOE guidelines.

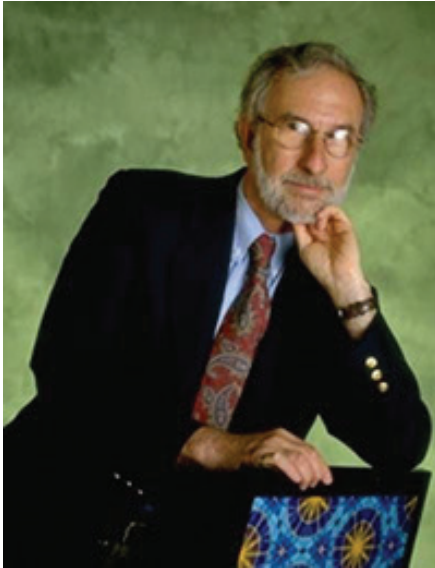


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Message from the Director



This year MBI celebrated the completion of its tenth year of programming. The emphasis year program for 2011-12 was *Stochastics in Biological Systems*, and it was a great success. Many thanks go to the program organizers for their efforts: Linda Allen, Rick Durrett, Tim Elston, Tom Kurtz, and Reinhard Laubenbacher. MBI celebrated its tenth anniversary in September 2012 with an exciting workshop *Math Biology: Looking at the Future*. The talks illustrated some of the many directions that math biology will be heading and most of these talks are archived on the MBI website.

MBI's missions include *Math -> Bio* and *Bio -> Math*. The first mission emphasizes the many ways that the mathematical sciences are used to clarify problems in the life sciences and the second emphasizes the ways that questions in biology are pushing developments in the mathematical sciences. This year's emphasis program highlighted the intertwining of these two missions within the area of stochastic modeling. The program also attracted a record number of long-term visitors to MBI.

The past year was a busy one for the MBI staff. In addition to the six emphasis year workshops and the six current topic workshops, MBI hosted three very successful education programs. The 2012 graduate summer school, operated jointly with NIMBioS and CAMBAM, was on *Stochastics Applied to Biological Systems*. In summer 2012 MBI experimented with a new and innovative undergraduate program in three parts: a two-week summer school in June, a distributed six to eight week REU program (with students going to seven participating Institute Partners), and a one-week capstone conference in August (which included a math biology graduate school fair). This program was so successful that MBI will continue it in 2013 with the intention of it becoming a staple of MBI education offerings. Finally, MBI hosted a *BioSciences Problem-Solving Workshop (PSW@MBI)*. Thanks go to the principal co-organizers, Jon Bell and Huaxiong Huang, for organizing this very successful event and to OCCAM and MPrime for their support.

Another MBI program has become a fixed point in our end-of-summer schedule: the *Workshop for Young Researchers in Mathematical Biology*. WYRMB is organized by the MBI post-docs, is aimed at researchers from advanced graduate students to untenured faculty, and serves the additional purpose of a networking conference. As expected, the eighth meeting of WYRMB was a great success.

MBI now has two distinctive diversity programs. The *MBI Visiting Lecturer Program* sponsors undergraduate level lectures by prominent mathematical biologists at institutions with strong minority enrollments. Information about VLP can be found at <http://mbi.osu.edu/about/vlprogram.html>. In 2011 MBI began a program of conference awards at meetings serving underrepresented minorities. The awards are of a best presentation sort (either poster or oral communication) and provide the winner with full support to attend one MBI meeting of their choice.

MBI's Early Career Award program finished its third year; it has been successful at attracting untenured assistant professors to be long-term visitors at MBI. Last year support was provided to five junior researchers to enable them to participate in the *Stochastics in Biological Systems* emphasis year program.

2011-12 witnessed a continued expansion in the MBI Institute Partner program. MBI now has 47 IPs. MBI very much appreciates the support it receives from these institutions, ranging from help in creating and choosing MBI programs to the mentoring of MBI postdoctoral fellows to participation in the new MBI summer REU program.

The MBI postdoctoral fellows program is very healthy with 18 post-docs in residence each year. The three year fellowships, coupled with the extensive MBI mentoring program, allows post-docs the chance to develop their own research programs before moving on. The *Tenth Anniversary Meeting* provided a chance for many of the nearly 70 MBI post-docs to get together and share stories.

As I do each year, let me end with an invitation. The MBI mission is to serve those who are working in one or more of the many interfaces between the mathematical sciences and the life sciences. With this in mind, we welcome community suggestions for programs that will help MBI to carry out its mission.



Institute Partners

MBI welcomes the participation of other academic institutions in the MBI Institute Partner Program. This program uses MBI matching funds to subsidize the travel expenses of IP member researchers to allow their participation in MBI programs.

In addition MBI supports 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.

Mentoring Program

Each MBI Postdoctoral Fellow has three mentors: a professional mentor from the MBI Directorate and two research mentors (one from the mathematical sciences and one from the biosciences). In a program begun in 2009 the research mentors may be either at Ohio State University or at one of partner institutions. Indeed, some MBI Postdoctoral Fellows had research mentors at Nottingham, Iowa, UC Irvine, Utah, and Virginia Tech.

The directory of research mentors can be found at the following web page:

<http://mbi.osu.edu/postdoctoral/mentoring.html>



Mission

To foster innovation in the application of mathematical, statistical, and computational methods in the resolution of significant problems in the biosciences;

To foster the development of new areas in the mathematical sciences motivated by important questions in the biosciences;

To engage mathematical and biological scientists in these pursuits; and

To expand the community of scholars in mathematical biosciences through education, training, and support of students and researchers.

Current Institute Partners

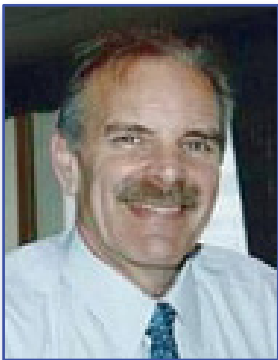
Arizona State University
Battelle
Boston University
Case Western Reserve University
Cornell University
Drexel University
Duke University
Florida State University
Howard University
IBM
Indiana University-Purdue University Indianapolis
Instituto Gulbenkian de Ciencia
Iowa State University
Michigan State University
Mississippi State University
National Tsing Hua University
New Jersey Institute of Technology
The Ohio State University
Ohio University
Penn State University
Princeton University
Texas Tech University
Trinity University
University of California at Davis

University of California at Irvine
University of California at San Diego
University of Cincinnati
University of Exeter
University of Georgia
University of Houston
University of Iowa
University of KwaZulu-Natal
University of Maryland at Baltimore County
University of Miami
University of Michigan
University of Minnesota
Universidad Nacional Autónoma de México
University of Notre Dame
University of Nottingham - CMMB
University of Oxford
University of Pittsburgh
University of Southern California
University of Utah
University of Washington
University of Waterloo
University of Wyoming
Vanderbilt University
Virginia Tech



MARTY GOLUBITSKY -DIRECTOR

The Director provides the scientific leadership, promotes the institution's mission and goals, and is responsible for the overall management and resource development of the institute. The director reports to the Board of Trustees.



MICHAEL REED -SENIOR SCIENTIFIC ADVISOR

The Senior Scientific Advisor designs and implements new programs that promote the mission of the Institute. The Senior Scientific Advisor will represent the Institute in the Director's absence.



HELEN CHAMBERLIN -ASSOCIATE DIRECTOR

Works with the director on diversity issues.



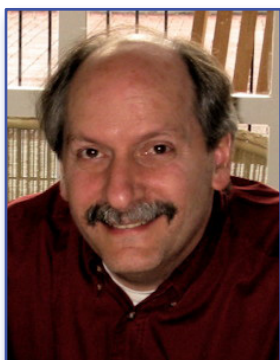
YUAN LOU -ASSOCIATE DIRECTOR

Responsible for the summer graduate program.



TONY NANCE -ASSOCIATE DIRECTOR

Oversees administration of the postdoctoral program and informational technology group, helps with scientific programming, acts as liaison with external evaluators, and helps with fiscal oversight and planning.



DENNIS PEARL -ASSOCIATE DIRECTOR

Responsible for the summer undergraduate program.



ANDREJ ROTTER -ASSOCIATE DIRECTOR

Provides leadership for relations between MBI and the Ohio State Medical Center, and chairs the MBI Colloquium Committee.



NIKKI BETTS -FINANCIAL AND HR MANAGER

Oversees daily operations and manages fiscal and human resource activities for MBI, including grant administration, budgeting, program planning and business operations. She also produces financial reports and oversees MBI's reimbursement/payment process.



SARAH HANCOCK -PROGRAM ASSISTANT

Coordinates housing and provides information to all MBI Long Term Visitors and Colloquium Speakers. Provides point of contact for all MBI visitors and assists Matt Thompson in processing travel and event coordination. Oversees MBI student workers.



STELLA CORNETT -WEB COMMUNICATIONS SPECIALIST

Manages the web site; handles all advertising including web and print; creates and distributes brochures, flyers, newsletters, posters, and annual report booklets; and receives participant abstracts and presentation materials and places them on the web.



CASEY JACOBS -PROGRAM ASSISTANT

Provides point of contact for MBI visitors and supports MBI programs, workshops, seminars and events. Assists with fiscal and procurement activities, processing travel reimbursements, event coordination and videography.



REBECCA MARTIN -OFFICE ADMINISTRATIVE ASSOCIATE

Provides direct office support for the Director; serves as primary point of contact for people within and external to the MBI; sends letters of invitation to all workshop and tutorial participants.



CARTER SCHOENFELD -SYSTEMS SPECIALIST

Provides support to users of MBI computer and presentation facilities, assists Michael with systems maintenance, and contributes to web programming projects.



MICHAEL SIROSKEY -SYSTEMS MANAGER

Responsible for technology at MBI, including maintaining and upgrading servers, desktop and laptop machines; handles hardware and software evaluation and procurement decisions; responsible for presentation and telecommunication facilities; provides support on space renovation project; and supervises web activity.



MATT THOMPSON -PROGRAM COORDINATOR

Manages event coordination, registration, and reimbursements; Assists in fiscal processing and human resources.



CHRIS REILLY -STUDENT WORKER

Provides critical logistic and clerical support for MBI events, including materials, advertising, and data management.



AMANDA SIROSKEY -STUDENT WORKER

Provides critical logistic and clerical support for MBI events, including materials, advertising, and data management.



ARJUN BERI -APPLIED MATHEMATICS, HOUSTON

Arjun's participation in the various working groups (initiated by P. Kramer and S. McKinley) here at MBI during the Spring 2012 has been extremely rewarding. Discussions on building an appropriate model for mitotic spindle dynamics have provided him with a good understanding of the complex process of cell division for eukaryotic cells. He has formulated an agent-based model for ants involved in territory exploration and foraging. Further, he has utilized notions from game theory to model interactions between ants involved in a territorial dispute (project in collaboration with D. Chowdhury and H. Jain). He has also extended his work on parametric estimation of stochastic models under indirect observability, and plans to collaborate with Greg Rempala on the problem of estimating parameters in a diffusion approximation to the jump process models representing concentration dynamics of molecules in a chemical reaction network.



DUAN CHEN -APPLIED MATHEMATICS, MICHIGAN STATE

With Guowei Wei (Michigan State) Duan continued his research in molecular biology: they finished a series of work on multiscale, multiphysics modeling, and simulation of proton transport through cell membranes. With Avner Friedman (MBI) he finished two projects; one is mathematical modeling of hypoxia inducible factors mediated tumor growth and the other is analysis of the free boundary problem of the tumor growth model. He plans to start a third project on stem cells with Tim Eubank in Medical Center at OSU. Starting next year he will continue to work on mathematical modeling and analysis of ion channels (microscopic) and tumor growth (macroscopic), but focus on the connection of these two-scale models. He believes that his research experiences in both proton channel and tumor growth will enable him to explore the role of structure-determined proton channel function in the whole process of tumor cell proliferation, apoptosis and angiogenesis.



SHU DAI -APPLIED MATHEMATICS, DUKE

Shu's research interests are currently in mathematical cardiology and slow axonal transport. He is collaborating with James Keener at University of Utah to consider the stochastic effect in the cardiac models, especially when the memory terms are significant. He is also working on a three-dimensional hexagonal lattice model for slow axonal transport of neurofilaments with Anthony Brown at Ohio State University and Peter Jung at Ohio University.



CASEY DIEKMAN -ENGINEERING AND BIOINFORMATICS, MICHIGAN

Casey's research interests are in mathematical neuroscience and biological rhythms. His work involves the application of dynamical systems theory to understand the master circadian (~24-hour) clock in the hypothalamus and the respiratory central pattern generator in the brainstem. Current projects include modeling the effect of photoperiod on the electrical activity of circadian clock neurons to determine how seasons are encoded, and developing a closed-loop model of respiratory control in response to hypoxia in premature infants. Additionally, Casey is using the theory of coupled cell systems to make predictions about network structure and the perceptual alternations observed in binocular rivalry experiments. He is also studying the role of astrocytic mitochondrial excitability in stroke through mathematical modeling and analysis.



MARISA EISENBERG -BIOMEDICAL ENGINEERING, UCLA

Marisa's research is centered on using and developing parameter estimation and identifiability techniques to build math models of human disease, on scales ranging from intracellular to epidemiological. Some of her current projects and collaborations include: algebraic methods for identifiability; cholera transmission dynamics; thyroid hormone regulation and disease; cellular invasion and migration in cancer; and determining cell cycle gene expression via time-series data deconvolution. These applications are wide-ranging, but share a common theme of modeling networks of complex, interacting components, each with particular data challenges and questions of interest.



JUAN B. GUTIERREZ -MATHEMATICS, FLORIDA STATE

Autocidal individuals are phenotypically and or genetically modified organisms that, when introduced into established populations at a certain rate, can cause local extinction. These organisms can be used for the control of invasive species. The Trojan Y Chromosome and the Daughterless Carp eradication strategies are examples of autocidal control of invasive species in which local changes to the sex ratio cause local extinction. Autocidal strategies can be formulated in terms of a cubic matrix, or covariance hypermatrix. Currently Juan is researching the properties of the cubic matrix that describes these systems, and he is trying to find ways to achieve unconditional eradication. Preliminary results show that the cubic matrix used forms a ring, and that destruction of a saddle-node bifurcation signals a new family of genetically modified organisms, that is, the biology of this problem pushes the limits of math, and the math of this problem pushes the limits of biology.



SAM HANDELMAN -BIOLOGICAL SCIENCES, COLUMBIA

Samuel Handelman uses phylogenetic methods to identify characteristics of biological sequences that confer different phenotypes. Dr. Handelman's novel method, GENPHEN, compares sequence differences between sibling lineages in much the same way that current methods compare actual brothers and sisters, to identify causal relationships while controlling for the genetic background. The table below shows five such sequence relationships identified in the envelope gene of HIV infecting a cohort of pregnant Malawian women, showing differences between transmitting (right) and non-transmitting (left) pregnancies.



FRANZISKA HINKELMANN -MATHEMATICS, VIRGINIA TECH

Franziska's research interest is in dynamic models in systems biology, with an emphasis on discrete models. Her research includes model inference, analysis, and optimal control. She uses polynomial dynamical systems as the mathematical framework for discrete models. This provides access to methods from algebraic geometry and computer algebra for model analysis. She is currently working on optimal control and bifurcation analysis for discrete models applied to problems in cancer systems biology.



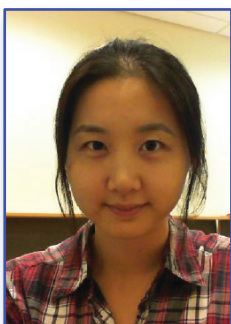
PAUL HURTADO -APPLIED MATHEMATICS, CORNELL

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.



HARSH JAIN -MATHEMATICS, MICHIGAN

Harsh's primary interest is in the application of dynamical systems to modeling cancer therapeutics. His current projects include a detailed biochemically motivated model of androgen ablation therapy in prostate cancer and its impact on mutation acquisition; the analysis of a nonlinear nonautonomous delay differential equation arising from a model of chemotherapy of ovarian cancer; and a multiscale model of endothelial cell-tumor cell crosstalk in head and neck cancers. Additionally, he is working on agent-based and PDE models of angiogenesis, and foreign body reactions.



HYE-WON KANG -MATHEMATICS, WISCONSIN-MADISON

Hye-Won's main research interests are mathematical biology, stochastic processes, and scientific computing. A major concern of her research is to apply and develop mathematical theories to model biological problems occurring in molecular biology, developmental biology, and biochemistry. Her professional aim is to construct mathematical models to understand problems in biology and to promote communication and collaboration between scientists and mathematicians in interdisciplinary areas.



RACHEL LEANDER -MATHEMATICS, TENNESSEE, KNOXVILLE

Rachel's research is in cell signaling and synchronization. *Francisella tularensis* is an intracellular pathogen that exploits crosstalk between toll-like receptor 2 (TLR2) and complement receptor three (CR3) to stimulate vigorous phagocytosis while inhibiting cytokine production. Many other intracellular pathogens including *Porphyromonas gingivalis* and *Mycobacterium tuberculosis* use CR3 to evade intracellular killing. *Francisella*, however, is distinguished by its reliance on complement. Rachel is constructing a mathematical model of membrane proximal TLR2 and CR3 signaling networks in order to evaluate interactions between them. Rachel is also working to identify network features that enhance synchrony. In this research she uses optimal control theory to study the relation between network heterogeneity and synchrony among nonidentical Kuramoto oscillators.



WING-CHEONG (JON) LO -MATHEMATICS, UC 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.



SUZANNE ROBERTSON -APPLIED MATHEMATICS, ARIZONA

Suzanne uses mathematical models to gain insight into problems in ecology, epidemiology and evolutionary biology. Some of her current work includes understanding the effect of heterogeneity and seasonality in transmission on the spread of waterborne disease, spatial distributions of aquatic predator-prey systems with adaptive movement, and how the risk of infectious disease influences habitat selection.



BLERTA SHTYLLA -MATHEMATICS, UTAH

Blerta is an applied mathematician who works on biologically inspired problems. Her research is primarily driven by scientific questions that arise in cell and molecular biology.



REBECCA TIEN -ECOLOGY AND EVOLUTIONARY BIOLOGY, CORNELL

Rebecca is interested in mathematical and computational ecology with applications to population dynamics, management and conservation of natural resources, particularly as they relate to aquatic ecology. She is currently working with Elizabeth Marschall and Yuan Lou on the biomagnification of PCBs and other heavy metals and their potential effects on food web interactions and population dynamics in Lake Erie.

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 meets annually to review the institute management and programs and to advise and approve the strategic priorities of the institute. More details at <http://www.mbi.osu.edu/committees/trustees.html>

Anna Barker
Arizona State University (12/31/14)

Rita R. Colwell
University of Maryland, College Park (12/31/13)

Irving Epstein
Brandeis University (12/31/14)

John Guckenheimer
Cornell University (12/31/11)

Kirk E. Jordan (Chair)
IBM T.J. Watson Research Center

Jim Keener
University of Utah (12/31/14)

Mark Lewis
University of Alberta (12/31/11)

Alan S. Perelson
Los Alamos National Laboratory (12/31/14)

John Reinitz
The University of Chicago (12/31/14)

Michael Waterman
University of Southern California (12/31/12)

Scientific Advisory Committee

The Committee consists of internationally recognized mathematical scientists and bioscience researchers from academia and industry. The Committee meets annually to review the institute programs, to suggest and decide on new annual programs, and to give advice regarding programmatic goals. More details at <http://www.mbi.osu.edu/committees/scientific.html>

Linda Allen
Texas Tech University (12/31/11)

Alexander R. A. Anderson
H. Lee Moffitt Cancer Center (12/31/13)

Paul Bressloff
University of Utah (12/31/13)

Thomas Chou
UCLA (12/31/14)

Chris Cosner
University of Miami (12/31/13)

Thomas Daniel
University of Washington (12/31/12)

Gerda deVries
University of Alberta (12/31/13)

Tim Elston
University of North Carolina, Chapel Hill (12/31/13)

Bard Ermentrout
University of Pittsburgh (12/31/11)

Greg Forest
University of North Carolina, Chapel Hill (12/31/13)

Shandelle M. Henson
Andrews University (12/31/14)

Trachette Jackson
University of Michigan (12/31/14)

Nan Laird
Harvard University (12/31/14)

Reinhard Laubenbacher
Virginia Tech (12/31/13)

Naomi Leonard (Chair 2011-12)
Princeton University (12/31/12)

Andre Longtin
University of Ottawa, Canada (12/31/12)

Sharon Lubkin
North Carolina State University (12/31/13)

Michael Mackey
McGill University (12/31/13)

Paul Magwene
Duke University (12/31/11)

L. Mahadevan
Harvard University (12/31/12)

Steven Rust
Battelle Memorial Institute (12/31/11)

Jack Tuszynski
University of Alberta (12/31/14)

Local Scientific Advisory Committee

The Local Scientific Advisory Committee 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. More details at <http://www.mbi.osu.edu/committees/local.html>

Irina Artsimovitch
Microbiology (6/30/14)

Janet Best
Mathematics (6/30/14)

Ralf Bundschuh
Physics (6/30/13)

James Cogdell
Mathematics (6/30/13)

Meg Daly
EEOB (6/30/12)

Andrea Doseff
Heart and Lung Research Institute, Molecular
Genetics, and Internal Medicine (6/30/14)

Martin Feinberg
Chemical Engineering (6/30/13)

Avner Friedman
Mathematics (6/30/12)

Erich Grotewold
Plant Biology (6/30/13)

Richard Hart
Biomedical Engineering (6/30/12)

Tim Huang
Center for Integrative Cancer Biology (6/30/14)

Kay Huebner
Molecular Virology, Immunology and Medical
Genetics (6/30/14)

Daniel Janies
Biomedical Informatics (6/30/13)

Doug Kniss
Obstetrics and Gynecology (6/30/14)

Stanley Lemeshow
Dean College of Public Health (6/30/12)

Gustavo Leone
Molecular Virology, Immunology, and Medical
Genetics (6/30/12)

Shili Lin
Statistics (6/30/13)

Thomas J Magliery
Chemistry (6/30/13)

Stuart Mangel
Neuroscience (6/30/13)

Elizabeth Marschall
EEOB (6/30/13)

Deborah Parris
Molecular Virology (6/30/13)

Roger Ratcliff
Psychology (6/30/13)

Wolfgang Sadee
Pharmacology 6/30/12)

Larry S. Schlesinger
Infectious Diseases, Microbial Interface Biology
(6/30/12)

Chandan Sen
Surgery (6/30/12)

Amanda Simcox
Molecular Genetics (6/30/12)

Parthasarathy Srinivasan
CSE, Biomedical Informatics (6/30/14)

Don Stredney
Biomedical Applications, OSC (6/30/12)

Joe Travers
College of Dentistry, Oral Biology Section
(6/30/14)

Ex Officios

Helen Chamberlin
Molecular Genetics

Marty Golubitsky
MBI

Yuan Lou
Mathematics

Tony Nance
MBI

Dennis Pearl
Statistics

Andrej Rotter
Pharmacology

MBI Diversity Committee

The MBI diversity mission is to help shape the mathematical biology community in a way that represents the diversity of our society. Historically, women, African-Americans, Hispanics, Native American, and Alaskan Natives have been underrepresented in the mathematical biology community. MBI works at two levels. First, it is MBI policy that each of its programs should actively seek diversity among its participants in gender and ethnicity. Second, MBI sponsors activities that promote mathematical biology and its opportunities in the academic community. To be most effective, these activities reach the undergraduate and pre-college levels, and contribute to increasing the diversity of future mathematical biologists. More details at <http://www.mbi.osu.edu/about/diversity.html>

Carlos Castillo-Chavez
Arizona State University (12/31/12)

Helen Chamberlin
The Ohio State University (ex-officio)

Joan Herbers
The Ohio State University (12/31/12)

Trachette Jackson
University of Michigan (12/31/11)

Yi Li
Wright State University (12/31/11)

Maeve McCarthy
Murray State University (12/31/13)

Aziz Yakubu
Howard University (12/31/13)





Visiting Lecturer Program

The Mathematical Biosciences Institute developed the Visiting Lecturer Program 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 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. 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. The phrase under-represented group is understood to mean African-Americans, Hispanics, Native Americans, and women. It is an important goal of the National Science Foundation to increase the participation of these groups in the sciences, so as to increase the strength of the American scientific workforce.

Department Chairs of a math sciences or a biosciences department can initiate discussions about bringing a Visiting Lecturer to their campus by sending an email to

Marty Golubitsky, Director
Mathematical Biosciences Institute
mg@mbi.osu.edu

The web page contains a list of visiting lecturers:
<http://www.mbi.osu.edu/about/vlprogram.html>

Visiting lecturer Talks

ERICA CAMACHO, MATHEMATICS, ARIZONA STATE UNIVERSITY

Talk @ Purdue University

Insights to Success Before, During, and After Graduate School Through My Story

Having grown up in East Los Angeles, California, Dr. Erika Camacho understands many of the struggles that students and women of color must endure in striving to attain their academic and professional goals. Dr. Camacho will be sharing her life experiences and the challenges she had to overcome to help her achieve her personal and professional goals. She will share stories about the key individuals and decisions that contributed to her success and transformation. Dr. Camacho will also share her passion for social activism and continual drive to transform the world of academia and strengthen our communities. Her life story is full of insights and lessons of empowerment for all.



Tracing the Progression of Retinitis Pigmentosa via Photoreceptor Interactions

Retinitis pigmentosa (RP) is a group of inherited degenerative eye diseases characterized by mutations in the genetic structure of the photoreceptors that leads to the premature death of both rod and cone photoreceptors. Defects in particular genes encoding proteins that are involved in either the photoreceptor structure, phototransduction cascades, or visual cycle are expressed in the rods but ultimately affect both types of cells. RP is “typically” manifested by a steady death of rods followed by a period of stability in which cones survive initially and then inevitably die too. In some RP cases, rods and cones die off simultaneously or even cone death precedes rod death (reverse RP). The mechanisms and factors involved in the development of the different types of RP are not well understood nor have researchers been able to provide more than a limited number of short-term therapies. In this talk I will give an introduction of the relevant physiology of the eye

as it pertains to RP and highlight some of the leading work in this area as well as existing mathematical models, including some of our work. In this research, we trace the progression of RP to complete blindness through each subtype via bifurcation theory. We show that the evolution of RP from one stage to another often requires the failure of multiple components. Our results indicate that a delicate balance between the availability of nutrients and the rates of shedding and renewal of photoreceptors is needed at every stage of RP to halt its progression. This work provides a framework for future physiological investigations potentially leading to long-term targeted multi-facet interventions and therapies dependent on the particular stage and subtype of RP under consideration. The results of this mathematical model may also give insight into the progression of many other degenerative eye diseases involving genetic mutations or secondary photoreceptor death and potential ways to circumvent these diseases.

2011-2012

Edward Allen
Texas Tech University

Linda Allen
Texas Tech University

Mino Belle
University of Manchester

Pascal Chossat
Université de Nice Sophia Antipolis

Debashish Chowdhury
India Institute of Technology

Bei Hu
Notre Dame

Adnan Khan
Lahore University

Peter Kramer
RPI

Vlastimil Krivan
University of South Bohemia

Tom Kurtz
University of Wisconsin-Madison

Reinhard Laubenbaucher
Virginia Tech

Dong Li
Iowa State University

Kang-Ling Liao
National Jiao Tong University, Taiwan

Rongsong Liu
University of Wyoming

Jon Mattingly
Duke University

Anastasios Matzavinos
Iowa State University

Scott McKinley
University of Florida

John McSweeney
SAMSI

Jihwan Myung
Hiroshima University

Seema Nanda
CAM/TIFR/ICTS

Greg Rempala
Georgia Health Sciences University

Joaquin Rivera-Cruz
Colgate University

Elissa Schwartz
Washington State University

Kajetan Sikorski
RPI

Ian Stewart
University of Warwick

Brandy Stigler
Virginia Tech

Peter Thomas
Case Western Reserve University

Zhi An Wang
Hong Kong Polytechnic University

Shari Wiley
Howard University

Yang Wang
Hangzhou Dianzi University

2012-2013

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Course Release

2011-2012

Mathematics

Janet Best
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Avner Friedman

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Yuan Lou
Joe Tien
Chuan Xue

Statistics

Radu Herbei
Shili Lin
Tao Shi

Joe Verducci
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Electrical and Computer Engineering

Terry Conlisk
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Kevin Passino

2012-2013

Mathematics

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Statistics

Radu Herbei
Laura Kubatko

Shili Lin

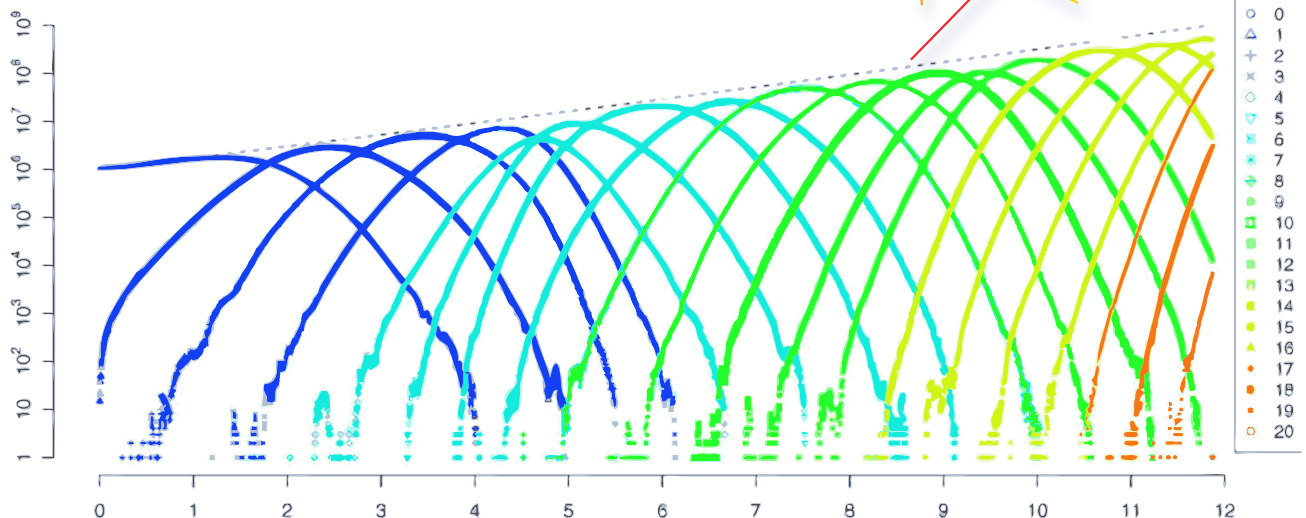
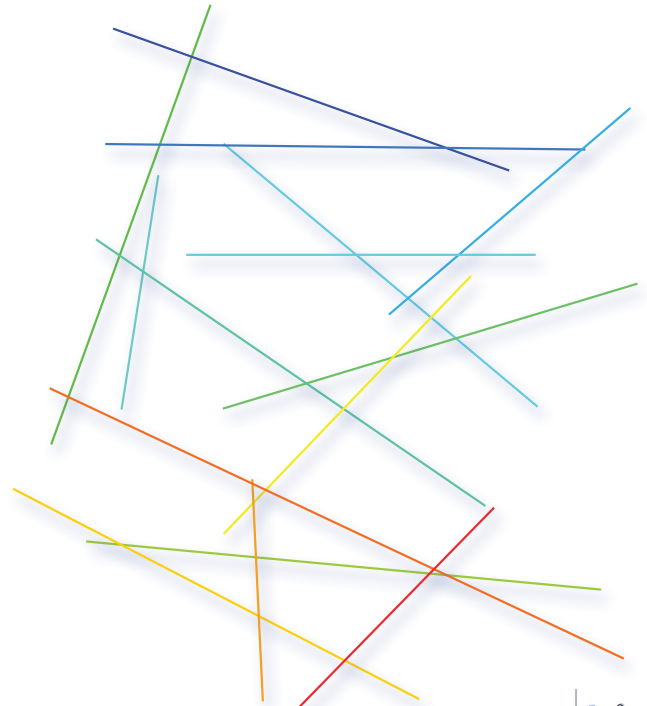
Computer Science and Engineering

Raghu Machiraju

Stochastics in Biological Systems

July 2011 - June 2012

Stochasticity is fundamental to biological systems. While in many situations the system can be viewed as a large number of similar agents interacting in a homogeneously mixing environment so the dynamics are captured well by ordinary differential equations or other deterministic models. In many more situations, the system can be driven by a small number of agents or strongly influenced by an environment fluctuating in space or time. Stochastic fluctuations are critical in the initial stages of an epidemic; a small number of molecules may determine the direction of cellular processes; changing climate may alter the balance among competing populations. Spatial models may be required when agents are distributed in space and interactions between agents form a network. Systems evolve to become more robust or co-evolve in response to competitive or host-pathogen interactions. Consequently, models must allow agents to change and interact in complex ways. Stochasticity increases the complexity of models in some ways, but may smooth and simplify in others.





Workshop I: New Questions in Probability Theory Arising in Biological Systems

September 12-16, 2011

Organizers: Richard Durrett, Thomas Kurtz, Peter March, and Ruth Williams

Report by: Duan Chen, Sam Handelman, and Franziska Hinkelmann

Monday/Tuesday

Pedigrees, genealogies and genomes

Nick Barton -Institute of Science and Technology, Austria

An individual passes on random segments of her genome to future generations: typically, after many generations, most of the genome is lost, but a small fraction survives, in many copies. This distribution of surviving blocks can be calculated using a branching process argument. Remarkably, after a few tens of generations it has the same form for every individual, with variation in reproductive value between individuals only affecting the probability of survival. These results follow the descent of genomes forward in time. The converse problem is to ask how far back we can reconstruct the pedigree, given a sample of complete genomes.

Noise in the nervous system

John A. White -University of Utah

Dr. John White talked about the nervous system, whose task is to generate internal representations of the world, in order to best interpret the present, predict the future, and pass genes to the next generation. However, the nervous system has a lot of noise. He began his talk with examples of numerous communications in brain function and then pointed out that sodium and potassium channels with noise dominate neuronal actions. White classifies the source of neuronal noise as noise (small), channel noise (medium), and synaptic noise (large). In his first talk he focused on the channel noise, described the phenomena and proposed the mathematical formulas. Uniform distribution and Langevin equations are utilized to study the channel noise, and it creates newly observable neural states.

Fluctuations in intracellular networks

Johan Paulsson -Harvard University

Dr. Johan Paulsson gave a general introduction to fluctuations in intracellular networks and corresponding mathematical tools, including motivation for his work and examples. He talked about the relevance of fluctuations in cells to losing information, and described sources of fluctuation like out of focus microscopy or slow maturation of fluorescent tags. Then he described the main mathematical model: a Markov process for dynamics that moves in random discrete steps in continuous time. A basic tool to study this kind of problem is the chemical master equation (or forward Kolmogorov equation). Exponentially distributed reaction times are assumed in studies of many fluctuation problems, including transmission of fluctuations between components, cell growth and divisions and near neutral stability of cells, etc. The relevance of fluctuations in cells was discussed. Alternatives to the Doob-Gillespie algorithm were introduced.

Wednesday

Cancer causes stable laws

Rick Durrett -Duke University

It is common to use a multitype branching process to model the accumulation of mutations that leads to cancer progression, metastasis, and resistance to treatment.

Durrett presented results about the time until the first type k (cell with k mutations), and the growth of the type k population and their use in evaluating possible screening strategies for ovarian cancer. The point process representation of the limit, which is a one-sided stable law, together with results from 10-60 years ago leads to remarkable explicit formulas for Simpson's

Emphasis Year Programs



Priscilla Greenwood

index and the size of the largest clone. These results are important in understanding tumor diversity, which can present serious obstacles to treatment.

A model for evolution in a spatial continuum

Alison Etheridge -University of Oxford

Dr. Etheridge described a framework for modeling populations distributed across a spatial continuum, producing what she terms a “Lambda-Fleming-Viot” (L-F-V) process. This model/process addresses three scenarios under which classical models of gene flow fail: the L-F-V process can explain patterns in data observed over large scales; the model of the L-F-V process predicts a level of genetic diversity closer to what is observed in real populations; and the L-F-V process tolerates non-independence between evolution at different genetic loci.

A simple mutational model that produces diminishing returns epistasis and decelerating fitness trajectories in adaptive walks

Paul Joyce -University of Idaho

Dr. Joyce addressed a fundamental conflict in modeling the impact of different genotypes on the fitness of an organism. Approaches that are readily tractable from a computational or analytical standpoint (additive and multiplicative models) do not generally agree well with the observed data. Joyce and colleagues proposed a “stickbreaking” model under which the fitness effect of one or more mutations is scaled according to a distance function. Results from simulations and theoretical analyses show a computationally and theoretically tractable approach with better agreement to available data.

Stationary distributions of stochastic delay differential equations with positivity constraints

Ruth Williams -University of California, San Diego

Dr. Williams gave an overview on problems of stochastic delay differential equations with positivity constraints and properties of their stationary distributions, including her excursion and motivation of research in mathematical biosciences. She introduced two examples, the biochemical reaction network and internet rate control, as problems of dynamics subjected to delay, variable non-negativity and intrinsic/extrinsic noise. She concluded that these problems could be modeled as multidimensional stochastic delay differential equations with normal reflection as analogue of a deterministic system with delayed feedback and positivity constraints,

then the existence and uniqueness of this type of differential equations need to be discovered. In their work, sufficient conditions for the existence and uniqueness of stationary distribution for such equations are obtained and the results are applied to an example of a simple biochemical reaction system.

Muller’s ratchet with compensatory mutations

Anton Wakolbinger -Goethe-Universität Frankfurt, Germany

Dr. Wakolbinger presented an alternative formulation of the classic Muller’s ratchet in which, when deleterious mutations accumulate, they can either be removed from the population by recombination (as in the classic Muller’s ratchet) or persist in the population in the presence of compensatory mutations. This model is formulated as a Fleming-Viot process with birth and death on the non-negative integers. This model can be solved in closed form, in the infinite population limit, by analyzing a probabilistic particle system that represents the solution of the system.

Thursday

Metagenomics and metrics on spaces of probability measures

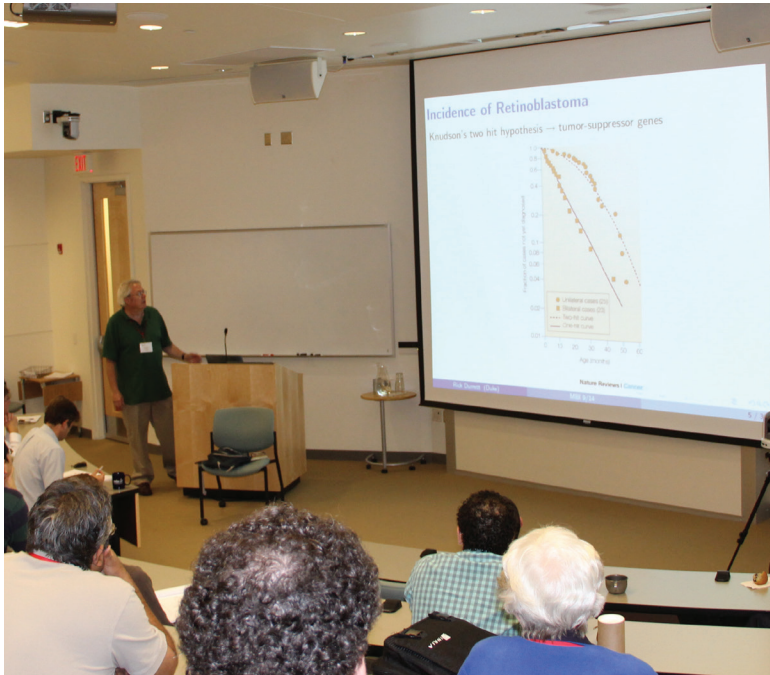
Steve Evans -University of California, Berkeley

Dr. Evans considered the question of how to distinguish the microbiomes of different groups of patients, healthy patients from diseased patients. Specifically, Evans considers the case of women with and without bacterial vaginosis. The microbiome of these women is measured using Metagenomics approaches, which sample the genetic material present in the microbiome of each patient, using high-throughput sequencing approaches. First, statistical methods are used to assign the sequenced DNA fragments to the most closely related organisms for which extensive sequence data is available. Steve Evans converts these organism-estimates into a cloud of points in a high-dimensional space, and presents methods to distinguish between assortments of such clouds (again, the set of diseased clouds versus the set of healthy clouds).

Random modeling of adaptive dynamics for sexual populations

Sylvie Meleard -École Polytechnique, France

Dr. Meleard and her collaborators studied models describing the evolution of a sexual (diploid) population with mutation and selection in the specific scales



Rick Durrett

of the biological framework of adaptive dynamics. They took into account the genetics of the reproduction. Each individual is characterized by two allelic traits and the associated phenotypic trait. The population is described as a point measure valued process with support on the genotype space. Its dynamics is a birth and death dynamics with selection and Mendelian rule in the reproduction and competition between individuals. Allelic mutations may occur during the reproduction events. The population size is assumed to be large and the mutation rate small. Assuming a good combination of the scales and small mutation steps, the coauthors proved that the population process converges on a long time scale by a jump process that jumps from one monomorphic homozygote equilibrium to another. This study involves a three-type diploid nonlinear dynamical system, which is studied using small perturbations of a neutral case. The behavior of the process is thus studied near the evolutionary singularities.

How to maximize neural complexity

Lorenzo Zambotti -Université Paris VI, France

In the context of this talk, the neural complexity of a family of random variables is defined as the average of the mutual information between different subsystems. This approach is intended to quantify the complexity of

a neural network. Lorenzo Zambotti presents results on how to maximize this complexity for networks of any given size, and the asymptotic behavior of the approaches (topologies, pairwise coupling constants etc.) that maximize this value. Intriguingly, the results Zambotti presents reflect both the differentiation (high entropy within each subsystem) and integration (high coupling between subsystems) that biology would lead us to expect might characterize such systems.

Cancer recurrence and escape dynamics

Jasmine Foo -Dana Farber Cancer Institute, Harvard School of Public Health

A new generation of anti-cancer drugs targeted to specific oncogenic pathways has emerged in recent years as a promising alternative to chemotherapy and radiation. However, the clinical success of such drugs has been limited by the evolution of acquired resistance, which leads to a relapse after initial response to therapy. A simple two-type branching process model to represent sensitive and resistant cells in a population was discussed. Based on her validated model, novel scheduling strategies in the treatment of non-small cell lung cancer with targeted therapy, which will delay resistance, were proposed. Instead of a uniform dosage, the model suggests giving a weekly high dosage, and several low doses. Using the large population limits of these processes in the time scale of extinction of the sensitive cell population, the turnaround point when the total tumor size goes from subcritical to supercritical (corresponding to the clinical time of disease progression), as well as the population levels of sensitive and resistant cells at various clinically relevant times were studied.

Dynamics of the evolving Bolthausen-Sznitman coalescent

Jason Schweinsberg -University of California, Santa Cruz

Dr. Schweinsberg introduces several different approaches to describing a population under the coalescent, and how to evaluate the time to the most recent common ancestor and the total length of the tree under these different models. Under the Bolthausen-Sznitman coalescent, the stable tree length has a stationary distribution, a generalized Ornstein-Uhlenbeck process, with a limit theorem in closed form. By coupling this stable process, time to most recent common ancestor can also be estimated in closed form.

Friday

*Probability problems arising in stochastic neuron models***Priscilla E. Greenwood** -University of British Columbia, Canada

Dr. Greenwood started her talk with a viewpoint of understanding neuron works on the basis of its output in response to a known input and introduced some different characteristics (such as bifurcation, or 1D and 2D examples of results convergences) between deterministic and stochastic models. Then she introduced the framework of deterministic and stochastic models in neuron models. She proposed the question that how a stochastic process move between the domains of attraction of locally stable points or cycles of an associated deterministic system and cross unstable cycles. Using the Morris-Lecar neuron model, she explained the bifurcation diagram, stochastic property and estimate of geometric distribution parameters of the model. She concluded that the much-studied interspike-interval distribution depends on a process exiting from a quasi-stationary state near a fixed point and crossing an unstable limit cycle. When a process encounters an unstable cycle, it tends to follow along a bit. In the quiescent period, the Morris-Lecar model behaves like a leaky integrate-and-fire model.

*Antibiotic resistance plasmids and spatial structure***Steve Krone** -University of Idaho

Dr. Krone first outlined that bacterial plasmids are circular extra-chromosomal genetic elements that code for simultaneous resistance to multiple antibiotics that are thought to be one of the most important factors in the alarmingly rapid loss of our arsenal of antimicrobial drugs. Then he gave a picture of plasmid transfer from donor to recipient and limited plasmid transfer on agar plates and biofilm. He also described the features that plasmids propagate horizontally by infectious transfer, as well as vertically during cell division. He proposed that spatial structure could play a key role in mediating the spread of antibiotic resistance genes since horizontal transfer requires contact between donor and recipient cells. Then he discussed ODE and stochastic spatial models of plasmid population dynamics, as well as empirical results. As an example of the effects of spatial structure, he used the spatial model to evaluate the effectiveness of a commonly used estimate of plasmid transfer efficiency when applied to surface-associated

populations.

*Identifying separated time scales in stochastic models of reaction networks***Thomas G. Kurtz** -University of Wisconsin-Madison

Dr. Kurtz introduced the methodology of identifying separated time scales in stochastic models of reaction networks because for chemical reaction networks in biological cells, reaction rates and chemical species numbers may vary over several orders of magnitude. He illustrated that if combined, these large variations can lead to sub-networks operating on very different time scales and separation of time scales has been exploited in many contexts as a basis for reducing the complexity of dynamic models, but the interaction of the rate constants and the species numbers makes identifying the appropriate time scales difficult. He introduced some systematic approaches to this identification, using Poisson process, time change representation for a Markov chain of abstract/general reaction network. This approach includes equations of system state, classical scaling/assumption and diffusion approximation. Finally, he applied this method to some complex reaction network models such as a viral infection and heat shock.



Jon Mattingly

Workshop 2: Stochastic Processes in Cell and Population Biology

October 24-28, 2011

Organizers: Timothy Elston, Thomas Kurtz, Johan Paulsson, and Mike Simpson

Report by: Hye-Won Kang, Wing-Cheong (Jon) Lo, and Blerta Shtylla

Monday

Fluctuations in Cells and Ecosystems

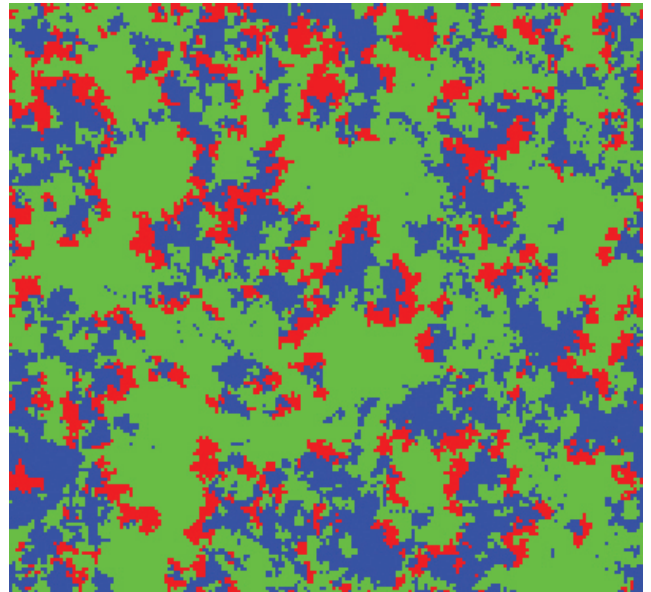
Johan Paulsson -Harvard Medical School

Dr. Paulsson considered how noise is transmitted and amplified (degraded) in systems with simple structure. He first showed a two-species toy model that involved production from a source, degradation, and degradation due to hetero-dimerization. He introduced intrinsic and extrinsic noise based on the source of noise and computed a coefficient of variation in terms of them. Expressing noise in terms of probability of complexity and mean for one of the species, he showed what kinds of kinetics contribute which noise.

Pathogen Extinction in Stochastic Models of Epidemics and Viral Dynamics

Linda Allen -Texas Tech University

In deterministic epidemic models, pathogen extinction in a population is determined by the magnitude of the basic reproduction number R_0 . In stochastic epidemic models, the probability of pathogen extinction depends on R_0 , the size of the population, and the number of infectious individuals. In the SIS Markov chain epidemic model, if the basic reproduction number R_0 is larger than 1, the population size is large, and $I(0) = a$ is small, then a classic result of Whittle (1955) gives an approximation to the probability of pathogen extinction: a/R_0 . This classic result can be derived from branching process theory. Dr. Allen applied results from multi-type Markov branching process theory to generalize this approximation for probability of pathogen extinction to more complex epidemic models with multiple stages, treatment, or multiple populations, and to within host models of virus and cell dynamics.



Three competing species in a specially heterogeneous environment.

Accelerated Stochastic Simulation Algorithm for Modeling Evolutionary Population Dynamics

Lev Tsimring -University of California, San Diego

Evolution and co-evolution of ecological communities are stochastic processes often characterized by vastly different rates of reproduction and mutation and a co-existence of very large and very small sub-populations of competing species. This creates serious difficulties for accurate statistical modeling of evolutionary dynamics. Dr. Tsimring introduced a new exact algorithm for fast fully stochastic simulations of birth, death, mutation processes. It produces a significant speedup compared to the direct stochastic simulation algorithm when the total population size is large and the mutation rates are much smaller than birth and death rates. He applied the algorithm on several examples such as evolution on a smooth fitness landscape, Kauffman's NK model,

directed evolution of a regulatory gene network, and a stochastic predator-prey system.

Effective Population Sizes and the Canonical Equation of Adaptive Dynamics

Hans Metz -University of Leiden

In structured population models one can graft evolutionary processes like random genetic drift or adaptive evolution by rare repeated substitutions of mutants in heritable traits affecting the state transition and reproduction processes of individuals. From this general perspective he derived a differential equation for evolutionary trait change under the additional assumption that mutations have small effect. In his approximation the rate of evolution is found to be the product of a parameter $n\{e,A\}$, which is equal to the population size times a dimensionless product of life history parameters, times the gradient of the invasion fitness of potential mutants with respect to their trait vector. From a heuristic connection with the diffusion approximation for genetic drift it follows $n\{e,A\}$ is equal to the effective population size from population genetics.

Cellular Decision-making in the Context of Population Dynamics

Guroel Suel, Pharmacology, University of Texas Southwestern Medical Center at Dallas

Dr. Suel's main question is how cells execute decisions to cope with and survive under environmental conditions. He found that stochastic fluctuations inherent to the biochemical reactions within genetic circuits can allow cells to cope with unpredictable environmental conditions. In addition, since cells have the ability to alter their own environment, the decisions at the single-cell level can depend on the context of the population.

Tuesday

Stochasticity in Circadian Clocks

Linda Petzold -University of California, Santa Barbara

Dr. Petzold talked about the circadian clock in mammals, coordinating timing throughout the body and entraining the body to daily light cycles. She gave an overview of how deterministic models can be transformed to stochastic ones. Experiments in which cell-to-cell signaling between neurons in the suprachiasmatic nucleus (SCN) is disrupted by physical separation of the cells, or by blocking vasoactive intestinal polypeptide (VIP) mediated

signaling, show that the remarkable precision of the circadian clock at the level of the organism relies on this intercellular signaling. In the absence of cell-to-cell signaling, each SCN neuron and the SCN as a whole exhibits a high degree of stochasticity, with significantly less stable oscillations. Dr. Petzold described new findings that were obtained from her group via a combination of experiment and discrete stochastic models, explored through wavelet analysis. Her talk brought about a nice discussion about how one might want to reset his clock to avoid jet-lag.

Computational methods for stochastically modeled biochemical reaction networks

David Anderson -University of Wisconsin-Madison

Dr. Anderson gave a very energetic talk on computational methods for stochastically modeled biochemical reaction networks. The simplest stochastic models of such networks treat the system as a continuous time Markov chain with the state being the number of molecules of each species and with reactions modeled as possible transitions of the chain. Dr. Anderson showed how different computational methods can be understood and analyzed by using different representations for the processes. The talk gave an excellent overview of various components used including approximation techniques, variance reduction methods, and parameter sensitivities.

Stochastic processes in the adiabatic limit: applications to biochemistry and population genetics

Ilya Nemenman -Emory University

Dr. Nemenman discussed stochastic kinetics with time scale separation. An important issue presented has to do with identifying the small variable. He showed how to integrate out the fast degrees of freedom, while rigorously preserving their effects on the fluctuations of slower variables. This procedure allows one to speed up simulation of kinetic networks and reveals a number of interesting phenomena, previously unobserved in the context of classical stochastic kinetics. One of the most interesting is the emergence of geometric phases, which he showed may have substantial effects, in particular on the frequency of fixation of new mutations in slower variable environments.

Simple, very simple, and not so simple models of populations lingering around a carrying capacity, and allowing evolutionary branching

Peter Jagers -University of Technology and University of Gothenburg

Dr. Jagers started by defining branching processes for population models. In a toy model of binary splitting branching processes with population size dependence, the chance of a little population establishing itself in the sense of reaching a band around the carrying capacity is determined, and so is the persistence time of the population. Furthermore, mutations and competition between morphs were introduced. The resulting processes exhibit evolutionary branching processes that occur in a manner slightly different from that predicted by established deterministic theory. In conclusion, Jagers mentioned that the studies of general cases of branching processes and the “fluid approximation” are ongoing for this work.

Kinetic equations in spatial quantitative genetics

Judith Miller, Mathematics, Georgetown University

Dr. Miller talked about the determination of a species' range related with geographical constraints, competitions among species, and limitations to adaptation. She introduced kinetic differential or integro-difference equations for the mean and variance of a quantitative trait (continuous random variable) as a function of space and time. In some cases, the equations recover known models and, in some other cases, obtain new ones that capture effects, such as non-monotonicity of traveling waves that can be seen in stochastic simulations. Kinetic equations due to Kirkpatrick and Barton for population range limits were reanalyzed, showing that they exhibit bi-stability and hysteresis. These suggest a possible mechanism for lag times between establishment and subsequent explosive growth and range expansion in the absence of an Allee effect.

Wednesday

From genome or organism to population -- and back again

John Yin -University of Wisconsin-Madison

Dr. Yin discussed cell-culture measurements and computational models used to understand how processes at the molecular and cellular scale govern the early dynamics of virus growth and infection spread. As a model system, he studied vesicular stomatitis virus (VSV), a rabies-

like RNA virus is growing on BHK cells. He noted that established single-cycle measures of virus growth within infected cells provide population averages, which mask potential cell-to-cell variation. Fluorescence-activated cell sorting was used to isolate single cells infected by single particles of a recombinant VSV expressing green fluorescent protein. Viral genetic variation and host-cell cycle differences were unable to fully account for the observed yield differences. Computer simulations of the VSV dynamics within an infected cell supported a potential role for stochastic gene expression to the observed yield variation. These studies are being extended to study the kinetics of virus production from individual infected cells.

Evolution in a spatial continuum

Amandine Véber -Centre de Mathématiques Appliquées, École Polytechnique

Dr. Véber described models for understanding the evolution of the genetic diversity of a population distributed over some continuous space. The novel idea of her work is that she phrases the evolution not in terms of individual reproductions, but a series of local events. She introduced the spatial Λ -Fleming-Viot (SLFV) process, a population model in which individuals live in a continuous space. Each of them also carries some heritable type or allele. The idea of this process comes from a model of panmictic populations. She described the large-scale behavior of this measure-valued process and that of the corresponding genealogical process of a sample of individuals in two cases: one that mimics the evolution of nearest-neighbor voter model (but in a spatial continuum), and one that allows some individuals to send offspring at very large distances. For the first case, a rescaled ancestral lineage converges to Brownian motion. For the second case, a rescaled ancestral lineage converges to symmetric α -stable process. Finally, she mentioned an extension of her studies including a selection mechanism, for example, by biasing the choice of the parent during a reproduction event.

Noise-driven decision making in HIV

Leor Weinberger -University of California, San Diego

Dr. Weinberger talked about the random behaviors of HIV infected cells, proviral latency vs. active replication. First, he introduced a background about the HIV latency decision. Transcriptional positive-feedback plays a critical role in determining HIV infected cell-fate by extend-



Gabor Balazi



Ellen Baake

ing the duration of Tat expression transients far beyond what protein half-life modulation can achieve. The experimental data showed that a minimal HIV Tat circuit drives the switch between different cell fates. Through studying the Hill coefficient, it supported that the transcriptional feedback is a stochastic timer switch but not a bi-stable switch. Also, reducing feedback enhances entry to proviral latency. He further discussed what kind of noise drives the timer switch. HIV promoter noise is a key for controlling fate determination. The studies of coefficient of variation showed that HIV gene expression is very noisy and occurs through randomly timed bursts of activity. The transcriptional bursting can generate high variability in HIV early gene products, which critically affect the viral fate-decision between active replication and proviral latency.

Establishing the genotype-phenotype connection for drug resistance

Gabor Balazsi -University of Texas MD Anderson Cancer Center

Dr. Balazsi talked about computational methods to predict the overall fitness of the cell population in arbitrary

antibiotic concentrations. Variation, heritability and selectability are required in evolution of natural selection. In this talk, he focused on studying variation related with genotype-phenotype connection.

Cells with identical genomes exposed to the same environment can differ dramatically in their gene expression and phenotype. The importance of such random phenotypic variation for stress resistance is now established, and Dr. Balazsi was interested in how the time-dependent aspects such as the duration of random cellular decisions affect sensitivity to drug treatment.

After briefly discussing how some gene circuits behave under noise effects, he talked about engineering *Saccharomyces cerevisiae* cells to carry a synthetic gene circuit controlling the expression of a bi-functional fluorescent reporter, yEGFP::zeoR, which also counteracted the antibiotic Zeocin. Single cells randomly differentiated into drug-resistant and drug-sensitive phenotypes, which differed in their fitness both in the presence and absence of drug. Through computational methods used to predict the overall fitness of the cell population in arbitrary antibiotic concentrations, he found that only after incorporating non-genetic (cellular) memory of randomly established drug resistance states, the antibiotic response of cell populations exposed to drug became predictable.

Population persistence in the face of demographic and environmental uncertainty

Sebastian Schreiber -University of California, Davis

Dr. Schreiber talked about how demographic (intrinsic) and environmental (extrinsic) noise can affect the long-term persistence of populations. Both biotic interactions and environmental fluctuations are key factors that can facilitate or disrupt persistence. Demographic stochasticity was studied by stochastic difference equations with countable state space. The long-term behaviors of the stochastic models are linked with quasi-stationary distributions that can be described by the attractors for deterministic models. Furthermore, environmental noise, for example the fluctuation of temperature, was studied with non-spatial multispecies models and spatially structured single species models with random variable parameters. Many species engage in competitive interactions, increasing the abundance of one has a negative effect on the other. Competitive

exclusion principle states that species using resources in the same way cannot coexist, but the coexistence of species is possible by a permanent failure to achieve equilibrium as the relevant external factors change that is related with the environmental uncertainty. Dr. Schreiber introduced invariant measure and average per-capita growth rate to find out the conditions that the system achieves stochastically persistent. Lottery models of competition and lottery models of rock-paper-scissor games support that coexistence is satisfied if the variance of the environmental noise is sufficiently large. In spatial models, regional persistence was studied through dominant Lyapunov exponent. This work can be extended with coupling the studies of two kinds of noise.

Thursday

Recombination dynamics and ancestral recombination trees

Ellen Baake -University of Bielefeld

Dr. Baake started the day by discussing recombination dynamics. She gave an overview over various models for the dynamics of the genetic composition of populations

evolving under recombination. She then focused on models involving only single crossovers in every generation and contrasted the situations in continuous and in discrete time. In continuous time, the deterministic model has a simple closed solution, which is due to the independence of the individual recombination events. In contrast, discrete time introduces dependencies between the links and leads to a much more complex situation. Nevertheless, the situation becomes tractable by looking backwards in time, starting from single individuals in the present of a Wright-Fisher population with recombination and tracing back the ancestry of the various gene segments that result from recombination. These segments become independent as the population size goes to infinity. She then identified the process that describes their history, together with the tree structures they define, called ancestral recombination trees. It turns out that the corresponding tree topologies play a special role. Surprisingly, explicit probabilities may be assigned to them, which then lead to an explicit solution of the recombination dynamics.

Cell-free synthetic biology in nanofabricated reaction devices

David Karig -Oak Ridge National Laboratory

Engineering living cells is notoriously difficult due to issues such as mutation, epigenetic variation, fitness effects, and the interaction of synthetic components with host cell processes. Thus, simpler contexts such as cell-free expression systems offer great promise to engineering complex biological behavior in a quantitative fashion. Furthermore, the confinement of cell-free gene circuit reactions in nanofabricated reaction devices offers a flexible approach to investigating fundamental aspects of gene circuit function. Dr. Karig discussed approaches in his research group to study gene circuit function in minimal systems with the goal of studying noise in simple gene circuits. Cell-free reactions confined in different volume wells are imaged over time using fluorescent microscopy. The noise characteristics of the resulting



John Fricks



gene expression trajectories are analyzed and compared for different gene circuits.

Bridging Scales in Molecular Motor Models: From Diffusing Heads to Multiple Steps

John Fricks -Penn State University

Dr. Fricks and his coworkers developed a new approach to modeling the details of molecular motor movement – namely a stochastic model for variable-length stepping of kinesins engineered with extended neck linkers. This model requires consideration of the separation in microtubule binding sites between the heads of the motor at the beginning of a step. The model can be used for the calculation of standard experimental quantities, such as asymptotic velocity and effective diffusion, through the appropriate limits of a semi-Markov process. Using this framework, asymptotic results for randomly detached motors are also obtained and linked to the statistical analysis of velocity data from motor assays. In addition, Dr. Fricks discussed how the framework developed in

his talk could be used as one component of a larger scale model for motor-cargo systems of the type presented in Dr. Kramer's talk later in the day.

Physico-Chemical Simulations of Eukaryotic Cell Motility

Garegin Papoian -University of Maryland

Dr. Papoian presented a three-dimensional, physico-chemical, stochastic model of sheet-like lamellipodia, which are projected by eukaryotic cells during cell migration, and contain a dynamically remodeling three-dimensional actin mesh. A number of regulatory proteins and subtle mechano-chemical couplings determine the lamellipodial protrusion dynamics. His work sheds light on how lamellipodial protrusion dynamics is affected by the concentrations of actin and actin-binding proteins. He also discussed molecular mechanisms of growth retraction cycles in filopodia, finger-like protrusions based on bundles of actin filaments. In particular, it was found that capping proteins and molecular motors may have a profound effect on filopodial dynamics. Other model

results relate to the rules of active transport in filopodia, mediated by molecular motors, allowing for highly efficient delivery of cytosolic proteins to the filopodial tip. Finally, this modeling approach could be used to examine the concentration profile of motors and actin along the filopodial tube, and the way motor transport couples to filopodial growth dynamics.

Bridging Scales in Molecular Motor Models: From Single to Multiple Motor Systems

Peter Kramer -Rensselaer Polytechnic Institute

Dr. Kramer followed up on the presentation of Dr. Fricks by discussing a coarse-grained model which resolves the spatial configuration as well as the thermal fluctuations of the molecular motors and the cargo. This intermediate model can accept as inputs either common experimental quantities or the effective single-motor transport characterizations obtained through the kind of systematic analysis of detailed molecular motor models described in Dr. Fricks' presentation. Through stochastic asymptotic reductions, he derived the effective transport properties of the multiple-motor-cargo complex, and provided analytical explanations for why a cargo bound to two molecular motors moves more slowly at low applied forces but more rapidly at high applied forces than a cargo bound to a single molecular motor.

Friday

Stochastic Fluctuation in Gene Circuit

Mike Simpson -University of Tennessee, Knoxville

Dr. Simpson's main concern was how gene circuit structure affects noise structure. He first introduced intrinsic and extrinsic noise. Using the simple auto-regulatory gene networks with the Hill functions, he concluded that a negative (positive) auto-regulation can decrease (increase) variance and correlation function. Using *E. coli* circuits, he showed that negative (positive) feedback gives shorter (longer) correlation. Then, he showed HIV circuits where HIV cells have two fates, infection and latency, and looked at how HIV gene circuits choose between two fates. By measuring the longer correlation time, he can conclude that there is a positive feedback in this circuit and also obtained the strength of the positive feedback. Finally, introducing a two-state transcriptional bursting model, he considered burst frequency and burst size using a noise mapping approach to understand these burst parameters.

Stochastic Problems in Pattern Formation and Development

Hans Othmer -University of Minnesota

Pattern formation in a developing tissue frequently involves the proper spatial localization of the boundary between different cell types, which is in general determined by concentration of morphogens produced at boundaries and diffusing to the tissue. How such boundaries between different cell types are set is an important issue in developmental biology. Stochastic models of this process are frequently based on reaction and diffusion equations, and Dr. Othmer addressed several questions related to the simulation of such systems. First, how does one choose a computational cell size for a complex reaction-diffusion network; secondly, how does one eliminate fast reactions in a stochastic reaction network; and thirdly, how does the network structure affect the resilience of boundary location determination when stochastic effects are important. Then he introduced high frequency processing which filters the low frequency noise, allowing him to concentrate on behavior of intrinsic in the gene circuit.

Stochastic Modeling of Cell Movement

Timothy Elston -UNC School of Medicine

Dr. Elston talked about stochastic models for random cell migration and for vascular tube formation. In cell migration, he is interested in rho-GTPase and how increasing or decreasing rho-GTPase affects cell migration. He introduced a simple stochastic model for cell migration with two variables for angle and distance assumed as independent Gaussian random variables and with random switch between active and inactive states of rho-GTPase. Using this model, he found interesting feature that increasing rho-GTPase lowers the velocity and at that time persistence is lowest. Next, he introduced a stochastic model of tube formation. He observed that CCM proteins cause degradation of rhoA GTPase and lower contractility. His model takes into account cell body shape, interaction with substrate, and how cells find each other considering protrusion. Using this model, he concluded that CCM deficient cell breaks more easily in the binding with the other cell and increasing rhoA GTPase increases contractility.

Workshop 3: Robustness in Biological Systems

February 6-10, 2012

Organizers: Frank Doyle, Richard Durrett, Arthur Lander, and Andreas Wagner

Report by: Hye-Won Kang, Rachel Leander, and Blerta Shtylla

Monday

Mechanisms of Homeostasis in Metabolic Systems

Fred Nijhout -Duke University

Dr. Nijhout discussed robustness of metabolic pathways that share enzymes and cofactors. He presented a physiologically-based mathematical model for folate-mediated one-carbon metabolism. This complex network provides the first steps in nucleotide synthesis, and the synthesis of S-adenosylmethionine, the universal donor of methyl groups for a host of methyl transfer reactions such as DNA and histone methylation, and the synthesis of glutathione, the universal antioxidant in animals. Regulation of stability in this network resembles physiological homeostasis. Homeostasis of critical biological functions requires a diverse set of dynamic biochemical regulatory mechanisms that cannot be deduced from examination of the biochemical reaction diagram. Dr. Nijhout and collaborators have found ten different homeostatic mechanisms that operate simultaneously to stabilize function against fluctuations in input and demand. Finally, he highlighted that homeostasis of critical biological functions is not the consequence of a stable steady-states, but instead requires continuous large, adaptive changes in some fluxes and metabolites.

A Dynamical Systems Approach to Resolve Cytokine Signaling Responses by Human T Cells

Neda Bagheri -Northwestern University

Dr. Bagheri explained how the efficacy of immune response depends, in part, on the types of cytokines secreted by activated T cells and their corresponding kinetic profiles. Using a procedure of serial microengraving, her experimental collaborators are able to quantify single and multiple T cell cytokine secretion dynamics, offering a unique multidimensional perspective to study time-dependent functional differences specific to im-

munophenotypes. Dr. Bagheri explained how they have employed dynamical systems strategies to these data to investigate the temporal evolution of specific cytokine responses that are indicative of a healthy immune system. Using these techniques, she described how they are able to better resolve and predict the nonlinear functional dynamics governing qualitatively different T-cell responses. Dr. Bagheri concluded by noting how this systems-level methodology may offer metrics to design more effective and personalized treatment strategies.

Noise Attenuation and Spatial Dynamics in Biological Systems

Qing Nie -University of California, Irvine

The focus of Dr. Nie's talk was on stochastic effects for spatial dynamics of complex biology systems. Dr. Nie explained how through modeling and simulations, one can study several general principles underlining noise attenuation and robustness in multiscale systems involving both intracellular and extracellular components. For several cases, existing and new experimental evidences that support their theoretical and computational results were presented.

Evolution of Robustness Formulated in Terms of Phenotypic Variances

Kunihiko Kaneko -University of Tokyo, Research Center for Complex Systems Biology

Dr. Kaneko discussed how by following an evolutionary stability hypothesis he and his collaborators could derive a general proportionality relationship between the phenotypic fluctuations of epigenetic and genetic origins. The relationship they derived suggested a link between robustness to noise and to mutation, since robustness can be defined by the sharpness of the distribution of phenotype. The proportionality between the variances was demonstrated to hold also over different phenotypic traits, when the system acquires robustness through the evolution. Finally, adaptation to environ-

mental variation was shown to require a certain degree of phenotypic fluctuations. Dr. Kaneko explained how all the obtained relationships were confirmed in models of gene expression dynamics, as well as in laboratory experiments. Finally, Dr. Kaneko discussed how consistency between evolutionary and developmental scales constrains developmental process and leads to universal laws on phenotypic fluctuations.

Robust Completion Time Distributions in Complex Biological Networks

Ilya Nemenman - Emory University

Dr. Nemenman gave an excellent overview of a biophysical framework for understanding biochemical processes that involve huge numbers of individual reversible steps, each with its own dynamical rate constants. He presented a characterization of the first passage time distributions for such processes. Further, he argued that, for a wide class of biochemical kinetics systems, the completion time behavior simplifies as the system size grows: it becomes either deterministic or exponentially distributed, with a very narrow transition between the two regimes. In both regimes, the dynamical complexity of the full system is trivial compared to its apparent structural complexity. This robust simplification of completion time distributions turned out to be independent of many microscopic details of the signaling systems and could be utilized for efficient control of cellular response properties.

Systematic Identification of Topologically Essential Interactions in Regulatory Networks

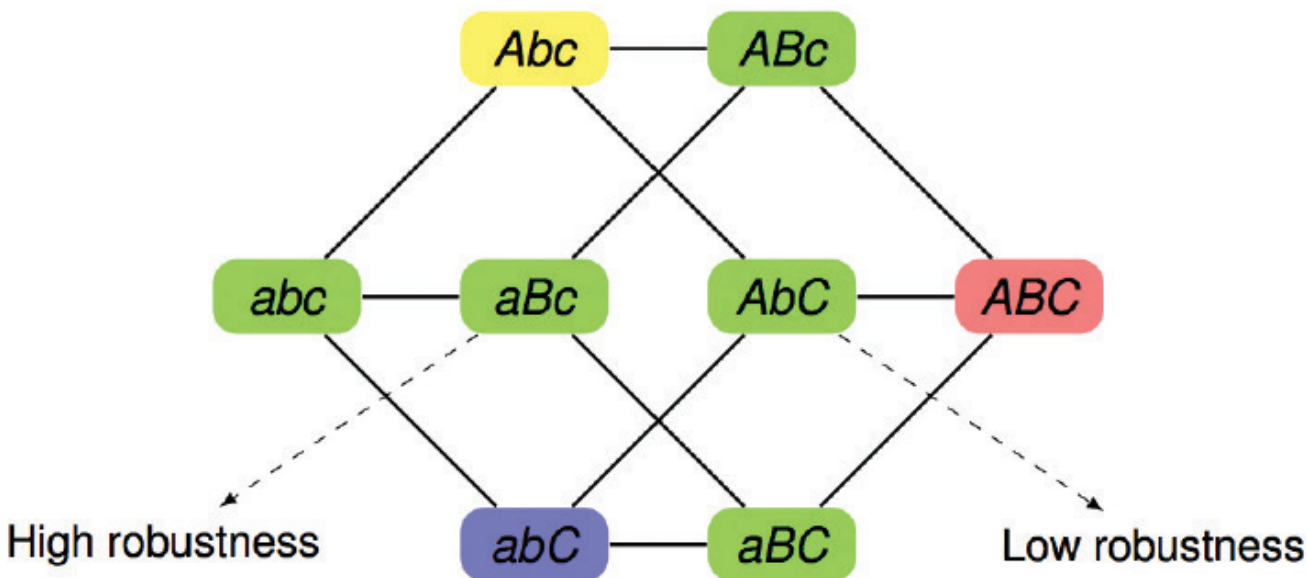
Maxim Artyomov - University of Washington

Dr. Artyomov discussed methods for deciphering the organization of complex regulatory networks. A problem with these networks is that perturbation assays cannot distinguish direct from indirect effects; he noted that the derived networks are significantly more complex than the true underlying ones. Discovery of the true network organization is a long-standing challenge and several approaches have been developed to infer regulatory networks based on gene expression data. Dr. Artyomov described his work on an approach for systematic analysis of network topology called Exigo. Exigo provides the means to identify core network structure for an input network of any topology with an arbitrary number of activating and inhibiting interactions. Finally, he discussed how Exigo allows for significant improvement in the network inference compared to DREAM top performers.

Using Noisy Inputs to Prevent Infant Apnea

Casey Diekman, Mathematical Biosciences Institute

Dr. Diekman gave an overview of his work on modeling infant apnea, which is defined as a pause in breathing for more than 20 seconds, can lead to oxygen desaturation and the need for resuscitation and assisted ventilation. Interestingly, a recent study has demonstrated



that continuously applied stochastic (randomly fluctuating) somatosensory stimulation stabilizes breathing patterns in preterm infants and can reduce apnea by approximately 65%. Dr. Diekman discussed his hypothesis that stochastic inputs to the respiratory central pattern generator (CPG) increase the dynamic range of the breathing rhythm in neonates. Dr. Diekman outlined his proposal to test this hypothesis through a combination of in vitro electrophysiology and computational modeling to understand the role of noise in the immature respiratory CPG.



Neda Bagheri

Tuesday

Genetic Versus Environmental Robustness

Aviv Bergman -Albert Einstein College of Medicine

Dr. Bergman began by explaining that certain phenotypes, for example the number of digits on a human hand and the number of whiskers on a dogs face, are remarkably insensitive to genetic and environmental variation. He then described his work involving a gene network model with feedback. He placed the model in an evolutionary context and measured its robustness. Surprisingly, he found that network robustness evolves even in the absence of stabilizing selection. During these investigations, Dr. Bergman also found that network connectivity supports genetic variation. Interestingly, when chosen at random, highly connected networks are the least robust, but after evolution, these networks are the most robust.

Dr. Bergman went on to describe a second model in which transcription factor binding sites undergo mutations. As a result of these mutations, the network's architecture evolves. Dr. Bergman examined how specific mechanisms, including silent mutations, mutations that alter transcription factor affinity, mutations that remove or create redundancy, and network rewiring mutations, influence the robustness of the network. He found that the ability of a specific mechanism to promote robustness is context dependent. In sparse networks silent mutations are an important source of robustness. In addition, sparse networks can gain robustness through mutations that alter the affinity of transcription factors. In large networks, mutations that alter network architecture are the primary source of evolved robustness. Redundancy, however, has little influence over robustness, in part because network redundancy is preserved throughout the evolutionary process.

Finally, Dr. Bergman discussed correlations between mutational and environmental robustness. Experimental observations suggest that these two types of robustness change together. However, this correlation would seem to be problematic for organisms that need to respond to environmental disturbances. He explored this scenario using Polycomb group proteins as a model system. For this system he found that epigenetics decouple environmental and genetic robustness, while causing the underlying genetic network to become simpler and more modular.

Stochasticity in Robust Developmental Tissue Refinement

Buzz Baum -University College London

Previously, we used computational modeling to explore the roles of mechanics and evolution in the generation of biological forms that withstand genetic and mechanical perturbations. Here I will present more recent work from my group in which we have used the dorsal thorax of the fly as an experimental system in which to ask similar questions during the refinement of a tissue prior to hatching. This has revealed a set of stochastic and noisy cell biological processes that contribute to the development of a well-ordered tissue from messy beginnings. I will briefly discuss the implications of these findings for our understanding of tissue homeostasis and disease.

*Robustness to Molecular Errors***Joanna Masel -University of Arizona**

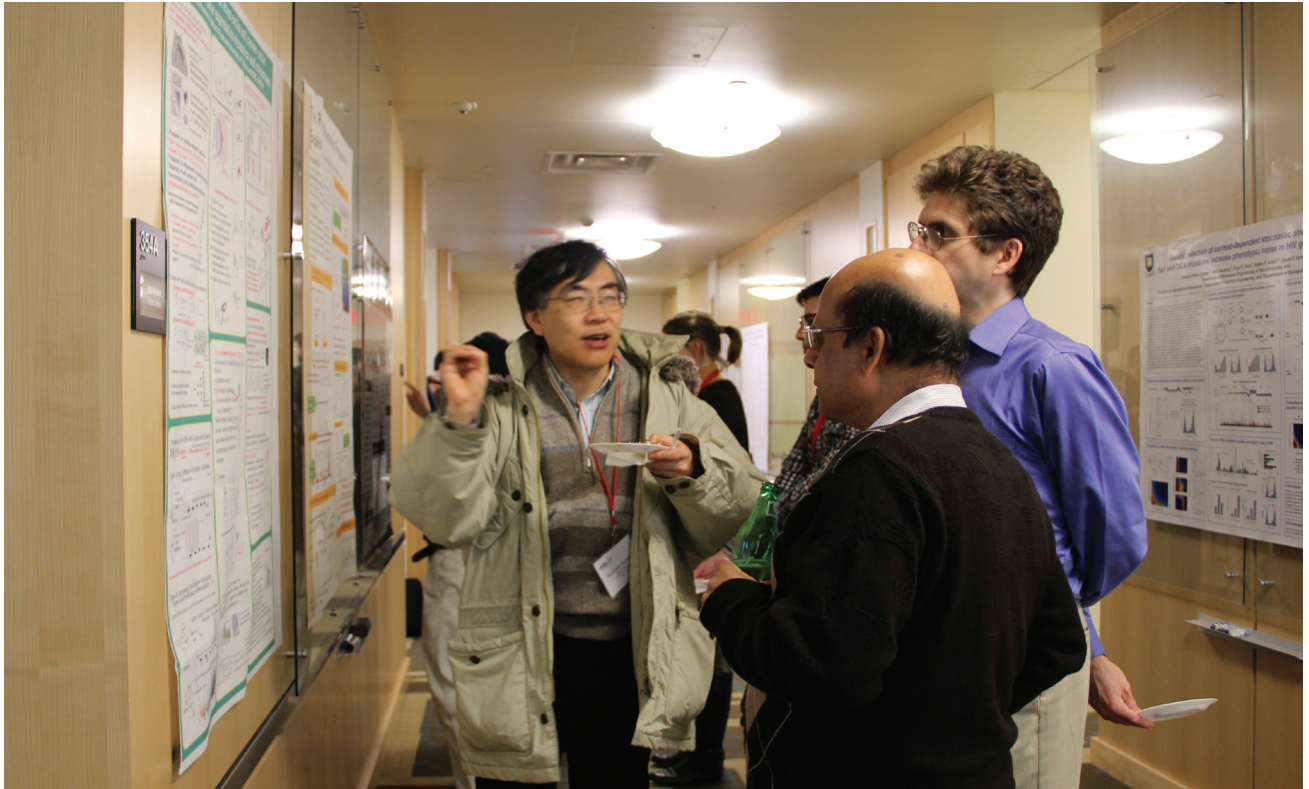
Dr. Masel's talk focused on the transcription and translation of proteins. She began by discussing the evolution of proofreading under a speed and accuracy tradeoff. Mistakes in gene transcription can be disastrous or inconsequential. Dr. Masel's described a model of protein transcription that is characterized by two parameters, the read through rate and the fraction of loci that are sensitive to read through error. She found that for large populations there are two optimal strategies. In one strategy frequent mistakes are managed through proofreading, in the other deleterious sequences are expressed and purged from the population's DNA. She compared the evolvability of these two strategies and found that the strategy in which many deleterious sequences are expressed is much more evolvable. She then explained that cryptic sequences, that is, sequences of DNA that are not usually expressed, may be co-opted if they have mild effects. In addition, when a trait is affected by multiple loci, a population that adapts this strategy can access multiple phenotypes even in the absence of genetic diversity. The number of phenotypes that can be co-opted from a single genotype is termed the neighborhood richness of the genotype. Dr. Masel went on to quantify the proportion of the phenotypic potential that can be attributed to neighborhood richness. Surprisingly, for a trait with multiple loci, neighborhood richness is the most significant source of phenotypic diversity. Numerical simulations showed that compensatory mutations drive the increase in phenotypic diversity. However, Dr. Masel also found that the likelihood that a network will arrive at a compensatory mutation decreases with the number of traits under consideration. In summary, Dr. Masel concluded that in order to achieve evolvability a population needs a minimum level of selection on cryptic sequences in order to purge out those that are deleterious, and very little selection beyond that so that compensatory mutations can drive evolution. Happily this balance is exactly that which evolves in the speed versus accuracy trade-off. In conclusion Dr. Masel discussed some specific examples of protein coding sequences that have evolved de novo from cryptic sequences.

*Robustness and Intragenomic Conflict***Jon Wilkins -Santa Fe Institute**

Dr. Wilkins began by explaining that evolution may be conceptualized as constrained and local optimization. He noted, however, that when multiple parties with conflicting interests are involved, a lack of cooperation can lead to suboptimal outcomes for both parties. Dr. Wilkins used the futile cycle involving IGF2/IGF2R to illustrate this phenomenon. Insulin like growth factor 2 (IGF2) is a growth factor expressed by fetal and placental tissues. Insulin like growth factor 2 receptor (IGF2R) does not transduce a signal in response to IGF2, but mediates its degradation. Dr. Wilkins explained that the rapid production and degradation of IGF2 is a futile cycle because the genes that control the expression of IGF2 and IGF2R are evolving under divergent selection pressures, that is, antagonistic coevolution. Dr. Wilkins explained this antagonistic coevolution is possible because IGF2 is subject to genomic imprinting, meaning that in each cell, the maternal and paternal copy of the gene are differentially expressed. This differential expression may be accomplished, for example, through methylation. In the case of the IGF2 gene, the maternal copy of the gene is silenced.

The current explanation for this imprinting rests on the idea that the fitness of an allele is determined by the number of copies of the allele that get passed on. In the placenta, the IGF2 gene balances the benefit of fetal growth with the cost of maternal depletion, as the health of the mother is essential to the progression of current and future pregnancies. It is hypothesized that the paternal copy of the allele is less concerned with long term damage to the mother's fertility that could affect future pregnancies than the maternal copy of the gene because the paternal copy of the gene is less likely to be passed on through the mother's future pregnancies (i.e. another male could father her children in the future). Imprinting of the IGF2 gene is thought to result from successive decreases in the expression of the maternal gene and increases in the activity of the paternal gene.

Dr. Wilkins went on to describe a simple mathematical model which indicates that imprinting reduces mean fitness and increases phenotypic variance. That is, in the presence of imprinting, extreme phenotypes are expressed at greater frequencies.



*Developmental Selection as a Mechanism of Robustness:
Implications for Genetic Assimilation and Life History*

Emelie Snell-Rood -University of Minnesota

Dr. Snell-Rood discussed a framework through which we can think about development and selective processes in development. She began by explaining that development may be highly deterministic or selective and context dependent. In deterministic development gene expression is triggered by external or internal stimuli and results in the predictable development of a trait. At the other end of the spectrum is developmental selection or somatic selection in which gene expression is associated with multiple phenotypes which are subject to selection. Developmental selection occurs in the immune system where a large initial set of antibodies are selected through interactions with antigens. Another example occurs in the nervous system where the broad innervation patterns characteristic of early development are selected through synaptic competition. In particular developmental selection occurs in muscular and sensory systems. Learning is another example of developmental

selection, for example butterflies learn to handle different flower types as they mature. In addition, stochasticity in gene expression is thought to contribute to developmental selection in response to variations in the environment. Although developmental selection is ubiquitous specific systems vary in their degree of sampling, and sensitivity to environmental feedback.

Dr. Snell-Rood then went on to explain the benefits and costs of developmental selection. Developmental selection supports robustness, improves performance in novel environments, and enables comparatively simple genotypes to support the creation of incredibly complex phenotypes. On the other hand, developmental selection is costly because the sampling process consumes time and energy. The costs of developmental selection result in a change in life history. For example across species of apes and butterflies learning is associated with a delay in reproduction. Species that exhibit strong developmental selection also tend to invest more resources in their offspring and live longer.

Finally Dr. Snell-Rood explained developmental selection has implications to responses in rapid man-made changes in the environment. It is often assumed that species with short generation times and high fecundity are better suited to deal with rapid environmental changes due to their potential for rapid evolutionary responses. On the other hand, species with delayed reproduction and low fecundity, which also exhibit strong developmental selection, may be equally well equipped to deal with rapid environmental changes. Hence Dr. Snell-Rood suggested that in identifying species likely to thrive in the face of rapid environmental changes one should consider the species capacity to produce both evolutionary and developmental responses.

The Control of Gene Expression and Noise in Embryonic Spatial Patterning

David Holloway -British Columbia Institute of Technology

Dr. Holloway discussed mechanisms of transcription and translation that support robustness in embryonic spatial patterning. In particular, he discussed a model of Bicoid-Hunchback protein expression in the anterior of a fly embryo. In this system, the Bicoid protein regulates expression of the hunchback protein. Although Bicoid protein expression decays exponentially from the anterior to the posterior of the embryo, Hunchback protein expression exhibits a sharp boundary. Dr. Holloway's model provides a mechanistic description of the regulation of Hunchback transcription, and a way to analyze the implications that Bicoid- and self-regulated Hunchback transcription have for the pattern of Hunchback expression. Mathematically the model consists of a system of stochastic ordinary differential equations. The model's predictions agree with experimental data in that RNA expression exhibits much greater relative variability than protein expression, and self-regulation reduces the sharpness and increases the noise in Hunchback expression. In addition, the model predicts that increasing the number and affinity of Bicoid binding sites can reduce Hunchback expression noise. Finally Dr. Holloway discussed an augmented model in which an additional protein Kruppel, inhibits Hunchback expression while Hunchback promotes Kruppel expression at low concentrations but inhibits Kruppel expression at high concentrations. This model shows that activator-inhibitor dynamics can sharpen expression boundaries.

Wednesday

Sex, Robustness, and Evolvability

Ricardo Azevedo -University of Houston

Dr. Azevedo talked about the relationship among sexual reproduction, mutational robustness, and evolvability. Mutational robustness is measured by probability that a mutation is not deleterious. It is widely believed that sexual reproduction selects for mutational robustness which promotes evolvability. Moreover, sexual reproduction can promote evolvability by causing long jumps through genotypes using recombination. In this talk, he asserted that over certain genotype networks, sex limits evolvability, since sexual reproduction may not select for the highest mutational robustness.

What Price Robustness?

Arthur Lander -University of California, Irvine

Dr. Lander talked about consequence of robustness, that is, how robustness or the evolution paths constrain the organization and behavior of biological systems. In general, robustness may constrain biological systems due to the following two factors: trade-offs among different types of robustness and inadvertent selection of epistasis. He analyzed three different kinds of models on tissue growth, pattern formation, and human disease to find under what situations, these constraints arise and how large their effects are.

Protein Domain Evolution is Constrained by Network Robustness to Rate Constant Changes

Ryan Gutenkunst -University of Arizona

Dr. Gutenkunst considered why different proteins evolve at very different rates, and investigated what factors determine a protein's rate of evolution. Dynamical robustness indicates how sensitive the network is as we change protein numbers. Based on the fact that protein domains with greater influence on network dynamics (with lower robustness) evolve more slowly, he suggested that functional importance and network robustness constrain protein evolution.

Epistasis Links Robustness to Adaptation

Jeremy Draghi -University of Pennsylvania

Dr. Draghi considered whether evolvability and robustness are incompatible. Mutational robustness produces greater neutral genetic variations and that is why robustness seems to be opposite of evolvability.

In this case, if these neutral variations are epistasis, populations can adapt faster. During adaptation, neutral variations interact with subsequent mutations, and he showed that this interaction between them links robustness and adaptation.

Lyapunov Exponent Analysis of an Extrinsic Apoptosis Signaling Network

Suzanne Gaudet -Genetics, Harvard University

Dr. Gaudet talked about cell to cell variability in cell death. Cells response differently in death-inducing ligands, and some cells require the mitochondrial outer membrane permeability (MOMP) to get to death. These factors and MOMP cause different cell death times and some of these cells may survive. In this talk, she considered the relationship between multiple factors determining timing of ligand-induced cell death and requirement of MOMP. Using Lyapunov analysis, a transient state of the signaling pathway to cell death can be investigated and sources of variability in cell death are studied.

Robustness and the Space of Possible Metabolisms

Andreas Wagner -University of Zurich

Dr. Wagner talked about how to study metabolic networks with a given phenotype in biology and one of the methods is to investigate the space of all possible metabolic genotypes. Since the space is vast and the space of the actual may be very different from the space of the possible, he suggested to study a sample space obtained in an unbiased way using Markov chain Monte Carlo methods. He concluded that metabolic networks are to some extent robust to mutation and environmental variability may help to explain the robustness of metabolic networks.

Thursday

Robustness and Evolvability in RNA Viruses

Paul Turner -Yale University

Dr. Turner considered evolution of mutational robustness based on the experimental results with RNA bacteriophage phi-6. Previously, he showed that virus co-infection is less robust, since it allows complementation which buffers the effect from mutation. Recently, it is shown that robust viruses evolve similarly but faster than the brittle ones and this fact indicates that robustness promotes evolvability. Here, he suggested that

this relationship is bidirectional based on the fact that prior selection for heat-shock survival causes viruses to evolve robustly as a correlated trait.

The Robustness Continuum: Yeast Cells Hedge Their Bets Against Unpredictable Environmental Change

Mark Siegal -New York University

Dr. Siegal talked about how much of the cell-to-cell heterogeneity reflects the noise tolerance of a robust system. He suggested that under some circumstances, heterogeneous traits might be favored over robust ones. As an example, he showed experimental results of yeast microcolonies after heat shock. After acute heat stress, only few cells in slowly growing colonies survive and all other fast growing colonies are dead. This experiment supports the idea that bacteria cell-to-cell heterogeneity can serve as a bet-hedging mechanism.

Robustness of Biological Oscillators

Stephanie Taylor -Colby College

Dr. Taylor talked about data analysis and a deterministic model of cell response and recover from encounter with Tetrodotoxin. Cell response shows oscillation behavior with cell-to-cell heterogeneity and it is regulated by mammalian circadian clock. She considered how robust oscillations of the clock are maintained even with noise and concluded that robust oscillations depend on both cells and network features. The next step would be how the period of the oscillations is determined robustly using the phase-base model.

Analysis of Context-dependent Stochastic Phenotypes in HIV-1 Latency

Kathryn Miller-Jensen -Yale University

Dr. Miller-Jensen began by explaining HIV latency. HIV prefers to infect activated T cells. Inside an activated T cell HIV replicates and causes cell death within 48 hrs. HIV can remain latent in Memory T cells. In these cells, HIV does not produce viral progeny, and hence is not susceptible to antiretrovirals. This is a major medical problem as it enables the infection to reseed after a patient discontinues antiretroviral therapy, and a medical mystery because HIV cannot infect memory T cells and it takes 2-3 weeks for an activated T cell to differentiate into a memory T cell.

Dr. Miller-Jensen used mathematical modeling to show that delayed transcription can explain memory T cell



Jensen concluded that mutations that increase the switching phenotype also alter amplification through the Tat transactivation circuit.

Robustness of the Cell Signaling Network as a Means to Discriminate Among the Different Models of Itk Kinase Regulation in T Cells

Sayak Mukherjee

Dr. Mukherjee began by explaining how T cells orchestrate adaptive immunity. T cells are equipped with cell surface receptors (TCRs) that bind to foreign peptides on the surface of antigen presenting cells. Receptor-peptide binding results in signaling for effector functions including cytokine release and differentiation. In addition to initiating a signaling response, T cells can remember previous challenges in order to

prepare themselves for similar insults in the future, and avoid mounting immune response to the peptides that occur naturally in our bodies.

Dr. Mukherjee went on to explain the process of thymocyte selection. T cells are generated in the bone marrow after which they migrate to the thymus gland where they undergo a maturation process called thymocyte selection. During this phase T cells begin to express TCRs. T cells which express TCRs that do not bind to endogenous peptides, or express TCRs with high affinity for endogenous peptides are deleted, while those T cells that express TCRs with moderate affinity for endogenous peptides are allowed to proliferate. The mechanisms through which maturing T cells are eliminated is not well understood, but recent experimental evidence suggests that the kinetic profile of T cell signaling may be an important determinant of the selection outcome. In particular, there are notable differences in the kinetics of T cell signaling in response to stimulation with endogenous and exogenous peptides.

Dr. Mukherjee's experimental collaborators showed that a soluble inositol (IP₄) controls the recruitment of Itk (a kinase which controls the selection outcome) and proposed a mechanism through which IP₄ fosters the initial recruitment of Itk to the cellular membrane while promoting dissociation of Itk from the membrane at later time points. Dr. Mukherjee used mathemati-

infection. In particular, HIV gene expression can be fit with a bursting model of transcription. In this model a gene promoter can exist in an active or inactive state. Bursting occurs when the promoter transitions to the active state. The model is described by two parameters, the burst size, which is the transcription rate divided by the inactivation rate, and the burst frequency. Interestingly, the burst size correlates with chromatin environment. The burst frequency, however, is an intrinsic property of the promoter. Experiments with Jurkat cells suggest that noisy gene expression leads to three distinct infection phenotypes; unproductive infections, productive infections, and a switching phenotype in which unproductive infections become productive over time. Mathematical analysis showed that the third phenotype when combined with feedback from a transcriptional activator (Tat) which alters the burst frequency and the inactivation rate can cause latency. In addition Dr. Miller-Jensen and her collaborators identified parameter values over which switching can result in latency.

Because the HIV promoter is highly regulated Dr. Miller-Jensen set out to discover mutations that would increase the frequency of switching. She found that mutations that increase the switching frequency also reduce transactivation through Tat. Dr. Miller-Jensen hypothesized that mutations that increase the switching phenotype would also alter basal expression dynamics. This was not the case. In fact, bursting dynamics of both mutations were only slightly different. Dr. Miller-

cal modeling to determine how specific interactions between these molecules contribute to the transient Itk response. In particular, he compared the ability of multiple mathematical models to reproduce experimental data on the dynamics of T cell signaling. In characterizing signaling dynamics, Dr. Mukherjee considered the amplitude, duration, and peak time of the response, as well as the ratio of the duration to the peak time (a measure of skewness). In the absence of experimental data about model parameters, Dr. Mukherjee deemed the best model to be that which was the most robust to parameter variation. Under this assumption the best model features IP4 mediated Itk recruitment.

Robustness in Pathogen-host Interactions and Dynamics

Chris Meyers -Cornell University

Dr. Myers began with a discussion of biological information processing and robustness to structural noise. That is, he addressed how specificity is maintained in the face of the potential for significant crosstalk between signaling networks. Experimental results have shown that in cellular signaling systems a receptor's ability to distinguish between ligands is essential for specificity. In particular, variable ligand affinity is not enough to support specificity. Motivated by a desire to see if it is possible for ligands to evolve specific binding niches, Dr. Myers formulated a distinguishing string selection problem. Dr. Myers showed that as the number of proteins competing for the same binding target increases the distinguishing string problem becomes more difficult to solve. In addition, the space of possible solutions becomes fragmented. That is, feasible solutions become more distant from each other. This has implications for speciation. In particular, it indicates that large scale mutational processes may be required to bridge the gap between distant solutions.

Dr. Myers then discussed the relation between network structure and dynamics. Focusing in particular on the relation between a model's network structure and the sensitivity/robustness of the model's dynamics to parameter changes in various directions. Dr. Myers and colleagues showed that a wide range of kinetic models exhibit both stiff and sloppy directions of parameter sensitivity. That is, a model's dynamics may be orders of magnitude more sensitive to parameters changes in some directions as compared to others. Moreover, stiff

parameter variations are determined by the eigenvalues of the Hessian matrix associated with the problem.

Dr. Myers went on to discuss three modes of plant-pathogen interactions. In the first mode, termed PAMP triggered immunity (PTI), a plant's immune response is triggered by pathogen associated molecular patterns (PAMPs) which are recognized by pattern recognition receptors (PRRs). In the second mode, termed effector triggered susceptibility, pathogens secrete effector molecules into the host cell in order to inhibit the plant's immune response. In the third mode, termed effector-triggered immunity (ETI), pathogen effectors trigger a strong secondary immune response which may result in apoptosis and the local loss of tissue. Many pathogens that have evolved the ability to disrupt PTI can also disrupt ETI. Indeed, as it was recently found that the mechanisms through which plants implement PTI and ETI are largely shared, the line between the two processes has become increasingly blurred. Dr. Myers then introduced some molecules that play prominent roles in mediating plant immune responses, including transmembrane PRRs, receptor-like kinases (RLKs) and resistance proteins with nucleotide binding-leucine rich repeats (R proteins with NB-LRRs). R proteins typically do not detect pathogen effectors directly instead they recognize the effects of effectors. In addition, plants may decoys or guards that function solely to entrap bacterial pathogens. These guards may be associated with specific R proteins. R proteins and bacterial effectors are subject to rapid evolution. Dr. Myers went on to summarize experimental results pertaining to the evolution of PTI, ETI, and effectors. These results led Dr. Myers to ask multiple questions, which he is just starting to address through simple genetic models.

Friday

Polyamine Biosynthesis and Translational Frameshifting in yeast: Characterizing a Cellular Feedback Controller

Declan Bates -University of Exeter

Dr. Bates explained how the polyamine molecules putrescine, spermidine, and spermine are involved in a number of important cellular processes such as transcriptional silencing, translation, protection from reactive oxygen species and coenzyme A synthesis. Polyamine depletion can cause apoptosis, and during development, defects leading to mental retardation



in humans (Snyder-Robinson Syndrome). Controlling polyamine concentrations is thus a significant regulatory challenge for the cell, because there are multiple cellular requirements for polyamines as well as a need to homeostatically maintain their concentration within a certain non-toxic range. In the cell, polyamine concentrations are regulated by multiple mechanisms, the most important of which is a negative feedback control loop involving *Spe1* and the protein antizyme. Dr. Bates described the first predictive model of the polyamine feedback controller, which has been developed and validated using a Systems Biology approach incorporating enzyme kinetics, control engineering and experimental molecular biology.

Biological Robustness: Implications for Systems Identification **Jörg Stelling -ETH Zurich, Basel, Switzerland**

Dr. Stelling presented his work on cellular network robustness. He detailed how widespread robustness of cellular networks, in principle, could make the systems biology task of identifying and characterizing cellular networks difficult because it implies potentially large uncertainties in parameters or topologies of mathematical models that quantitatively capture the network behavior. Yet, robustness may be exploited in systems identification as an additional criterion for the plausibility of a given model. In both cases, Dr. Stelling highlighted that quantitative characterizations of system robustness to perturbations are needed. The talk then focused on implications of robustness on systems iden-

tification with a focus on metabolic networks. Using the network structure and assumptions on optimal rejection of perturbations alone, Dr. Stelling and collaborators developed a method to analyze sensitivities in metabolic reaction networks that can be directly linked to, for instance, variability in gene expression. In an application to global data sets on the reaction of *Bacillus subtilis* to changes in nutrient source, the method revealed qualitatively different, large-scale responses to apparently simple, symmetric perturbations. Finally, Dr. Stelling emphasized that general methods for quantification of robustness, in addition, are becoming feasible by using probabilistic approaches, which may ultimately provide principled insight into the role of robustness for the identification of cellular systems.

Robustness in Intracellular Transport

Scott McKinley -University of Florida

Dr. McKinley discussed robustness in the context of cellular molecular motor transport. Modeling of these molecular motor action can focus on various scales, such as nanoscale, micron, or millimeter phenomena. For each scenario stochastic effects are important. The issue of robustness appears in various contexts such as for transport accomplished by teams of motors. Even though it seems that these motors are not locally controlled, their collective behavior is surprisingly robust at the micron scale arranging for precise cargo delivery and complex cytoskeletal network organization. An important question remains how motors that have varying individual properties can collectively produce robust behavior to move cargo in a specific direction. Dr. McKinley described mechanisms by which such regulation could be obtained such as tug-of-war or precise protein action. Robustness can also be understood in the context of axonal transport phenomena, where cargo transport by teams of molecular motors produces robust patterns of axon component distributions. Dr. McKinley described his work on a probabilistic micro-scale compartmental axon model and how this model can be used to study macro-scale properties of axonal transport. Using techniques from probability theory, asymptotic limits of the stochastic behavior of individual motor-cargo complexes could be computed. Finally, Dr. McKinley showed how model analysis yielded tools for measuring robustness in the context of equilibrium cargo distributions in the axon.

Workshop 4: Evolution and Spread of Disease

March 19-23, 2012

Organizers: Linda Allen, Sally Blower, Sylvie Meleard, and Helen Wearing
Report: Suzanne Robertson and Rebecca Tien

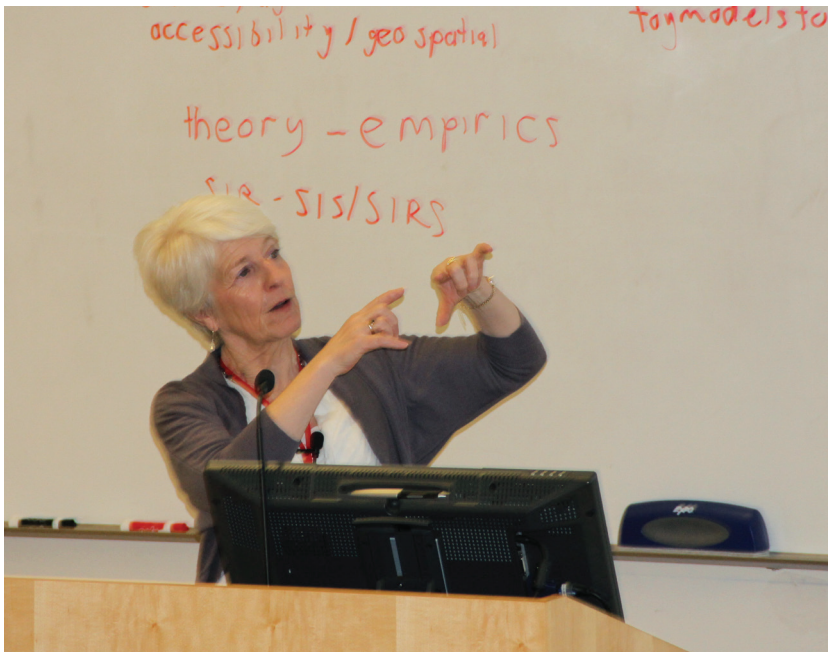
Monday

Real time numerical forecast of global epidemic spreading

Alessandro Vespignani -Indiana University

Dr. Vespignani focused on the use of large-scale computational models for making public health projections and decisions. He discussed the GLEaM (Global Epidemic and Mobility) model, which generates stochastic realizations of the spread of epidemics worldwide allowing him to gather information on disease prevalence, morbidity, number of secondary cases and number and date of imported cases for 3,360 subpopulations in 220 countries with a time resolution of 1 day. He used this model along with demographic and mobility data to make projections for the 2009 H1N1 pandemic by estimating

the transmission potential and the relevant model parameters with a Monte Carlo likelihood analysis. He used data collected in 46 countries of the Northern Hemisphere during the course of the pandemic to conduct an extensive validation analysis of these results, successfully predicting the timing of the outbreak in most cases and explaining why the model predictions were off in the remaining cases. The challenges posed by the real-time estimation of parameters needed for this model, the different levels of data-integration and model validation through high quality data sets were also discussed. Examples include determining the level of detail in data, such as commuting patterns and human mobility data, needed for accurate predictions as well as how to obtain and incorporate data on social behavior, such as adaptation to risk.



Valerie Isham

Ro and other reproduction numbers for epidemic models with households and other social structures

Frank Ball -University of Nottingham

The basic reproduction number R_0 , the expected number of new infections produced by introducing a typical infected individual into a completely susceptible population, is one of the most widely used measures for quantifying the spread of disease in epidemiology. However, it is not clear how to define this quantity for populations with explicit social structure; many threshold parameters have been considered in the literature. In this talk, Dr. Ball first considered the Households Model, which includes local within-household mixing as well as global between-household mixing. He uses branching processes to define and calculate R_0

for this model, and then compares this measure to other threshold parameters in the literature, noting these comparisons can be used to compute sharper bounds for the fraction of the population that must be vaccinated to prevent a large outbreak. The comparisons also imply that if $R_0 > 1$, previous estimates of critical vaccination coverage (vaccinating a fraction $1 - 1/R_0$ of the population, chosen uniformly at random, with a perfect vaccine) are no longer sufficient. Dr. Ball concluded his talk by extending his model to incorporate the additional social structure of workplace units as well as household units.

Weighted networks with applications to epidemics

Tom Britton -Stockholm University

Dr. Britton introduced the configuration network model and presents an extension in which edges are weighted (depending on the degree of adjacent vertices), along with some asymptotic properties of this model. He considers stochastic processes taking place on the networks, such as the spread of an epidemic where the probability of transmission may depend on the weight of edges. Results were presented for cases where weights of edges represent number of days patients spent in the same hospital ward in Stockholm (modeling the spread of mrsa), the number of households with a member in each workplace in Sweden (for influenza), and the number of sexual contacts (for STDs). The basic reproductive number R_0 for each model is computed and compared to that of a network with weights randomly reshuffled among edges, finding that reshuffling can either decrease or increase R_0 . For the sexual network, the actual network has a lower R_0 than the random network, as individuals with many partners tend to have fewer contacts with each partner. Dr. Britton also considered the case of individual heterogeneity, where nodes may differ in infectivity and susceptibility. He found that a positive correlation between infectivity and susceptibility increases R_0 , while a negative correlation can have the effect of homogenizing the population and reduce R_0 .



Limit Theorem for a SIR Model of a Random Graph

Jean-Stephane Dhersin -Universite Paris

Dr. Dhersin considered a SIR epidemic model on a random network generated by the configuration model, in which the degree distribution of the vertices is specified and the edges are matched up randomly. He presented three measure-valued equations that describe the evolution of the epidemic, specifically the degrees of the susceptible individuals and the number of edges from an infectious or removed individual to the set of susceptibles. These three degree distributions are sufficient to describe the course of the disease. Dr. Dhersin investigated the limit for large population size, and he showed a system of stochastic differential equations converge to a limit satisfying the deterministic equation. This also provides a rigorous proof of the set of equations obtained and proposed by Volz, for which the proof was previously open.

Analysis of the Cuban HIV Network

Viet Chi Tran -Universite des Sciences et Technologies de Lille

The Cuban HIV database has data for over 25 years of cases, ever since HIV was introduced in the country in 1986. Contact-tracing has been used since the beginning of the epidemic in an effort to detect more HIV-positive individuals and control the spread of HIV. The data from

this program can be used to provide information as to the social networks underlying the propagation of the disease, reconstruct the history of transmission, and make predictions to evaluate public health policies and prevention strategies. In this talk, the Cuban contact-tracing network was presented, consisting of 5,389 individual nodes and 4,073 edges, with almost 2,000 isolated individuals or couples and a giant component of 2,386 nodes. This network was analyzed and possibilities for modeling HIV in Cuba based on this network were discussed.

Tuesday

An introduction to stochastic models for epidemics and the effects of population structure

Valerie Isham -University College

Dr. Isham presented an overview of modeling epidemics, focusing on model structure and modeling issues. She began by reviewing the motivation and historical background of mathematical epidemiology. After presenting the deterministic as well as stochastic SIR models, she discussed ways in which heterogeneity has been incorporated into such models, including intrinsic host variability such as gender or age, mixing rates, and contact networks. She also presented R_0 and related threshold quantities that have been developed for these models. Dr. Isham next discussed incorporating population structure into epidemic models, concentrating on population networks and the effect of different network structures (including simple random graphs, scale-free networks, and random geometric graphs) on the dynamics of the epidemic, including the threshold for an outbreak and widespread transmission of the disease as well as the final outbreak size.

Modeling and inference for healthcare-associated infections

Philip O'Neill -University of Nottingham

Dr. O'Neill discussed one infection in particular, methicillin-resistant *Staphylococcus aureus* (MRSA), which is a bacterium responsible for several difficult-to-treat infections in humans. Two case studies involving data from hospitals in Boston were used to generate transmission models, and their accompanying applications were also discussed. Infections can be quite costly from an economic perspective so there is a lot of interest in understanding some of the following questions: Do control measures work? What is the risk acquisition related



to the number of carriers? What particular strains are present in a population of?). In the first study, hospital data included information such as patient level, admission/discharge dates, dates of tests and their outcomes, patient location [isolated or not?], and antibiotics administered. Stochastic models were used to describe indirect transmission between individuals and important parameters such as rates (e.g., colonization) and probabilities of certain events of interest were estimated. The second study looked at a group of patients who tested positive for MRSA and were isolated (use of surgical masks, gloves, etc.). Here they looked at the effectiveness of isolations on disease transmission using an MCMC model that included both isolated and unisolated groups of colonized individuals.

Disentangling the spatio-temporal dynamics of the 2009 A/H1N1 influenza pandemic in Mexico and Peru

Gerardo Chowell-Puente -Arizona State University

Dr. Chowell discussed the variability and timing in waves of the 2009 A/H1N1 influenza pandemic (e.g., U.S. and Mexico experienced multiple waves, while S. Hemisphere only a single wave). He looked at the role of multiple variables (population factors, travel patterns, climate, geography, school cycles, and control interventions) from three different regions in particular: Mexico,

Peru and Chile. One particular area of focus was the impact that school closure periods in these three countries had on the spatial patterns of pandemics waves and seasonal variation in waves. The main results across all regions were that 1) there was a significant association between the winter school vacation period and incidence rate and 2) temperature and specific humidity were correlated with local transmissibility and pandemic timing.

Modeling the diversity and stability of human vaginal microbial communities

Jose Miguel Ponciano -University of Florida

Dr. Ponciano discussed population growth of vaginal microbial communities based on data. All data were collected from women who were trained for self-testing and the models generated from this data look at how covariates can lead to changes in dynamics of the system. Several different modeling approaches were discussed, in particular the following: a model where the matrix of species interactions remain constant across women, a woman specific dynamic parameters model where each community within each woman has its own unique dynamics OR an across-women dynamic parameter model where individual communities within women were clustered and the 4 sub-models above were also possible. Some other questions of statistical interest that his research covered were whether or not the model parameters are identifiable and if the matrix of interactions analogous to the tree topology in phylogenetics.

Contact networks for modeling immunizing infectious disease dynamics

Shweta Bansal –Penn State University

Dr. Bansal discussed invasion dynamics (e.g., SARS) and how naturally-acquired immunity restructures the host population. Recurrent epidemics are a frequent occurrence and can lead to partial immunity. Of interest is how immunity impacts population contact structure, what the consequences are for future outbreaks, and dynamics. Dr. Bansal discussed two types of immunity, Perfect and Partial and their differing impacts on population structure. Dr. Bansal found that pathogen spread in a naïve pop makes contact structure sparser and homogeneous; pathogens can easily re-invade heterogeneous populations, however the epidemiology outcome is less dire; there exists more evolutionary pressure in

a homogeneous population to evolve immune escape variants or more contagious strains.

The last part of his talk looked at a case Study on the H1N1 epidemics in 2009. He found distinct difference in susceptibility across ages. Initially, children are more vulnerable so when the first wave of the epidemic hits, they are affected more. However, because adults have less connectivity than children, in a post-epidemic period, risk shifts from children over to adults (larger percent of children have immunity after first outbreak). One solution for controlling outbreaks based on this case study is to rethink the vaccination strategy to wipe out future epidemics.

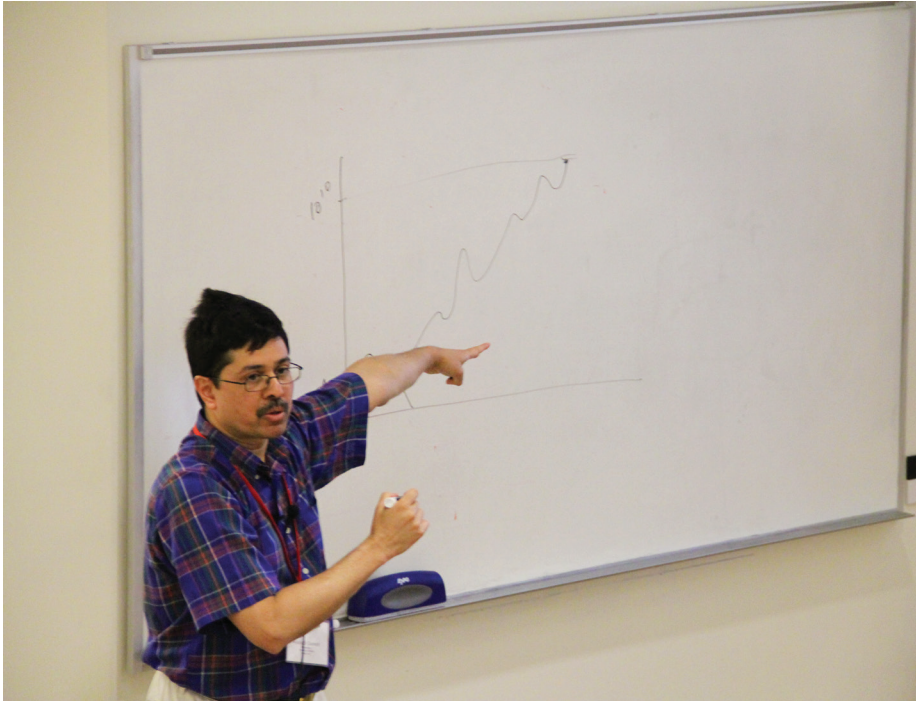


Wednesday

The interplay of infectivity that decreases with virulence and limited cross-immunity: (toy) models for respiratory disease evolution

Hans Metz -Universiteit Leiden

Dr. Metz started his talk with an introduction of the Anderson-May model on the evolution of virulence and its limitations. One important downfall of the original model, is that it makes the simplifying assumption that there is a negative trade-off between disease-induced mortality rate and infectivity and that the disease is well-mixed within the body of the host. This single as-



Ayalvadi Ganesh

sumption can have profound impacts on the accuracy of the model, because in reality, both the severity to the individual as well as the infectivity of the disease depends on the location in the body where the pathogen is found.

After spending the bulk of his talk reviewing the basics of adaptive dynamics, Dr. Metz discussed a model which assumes heterogeneous spread of the pathogen within the host body. In particular, he looked at modeling a respiratory infection in which a pathogen can be found anywhere along the pathway between the alveola of the lungs and the inner lining of the nose and its location is described by its phenotype, x . He found that pathogen that lay deep within the body was more damaging to the individual, but less infective while the reverse was true for pathogen found within the nasal passages. From an evolutionary perspective, the deeper in the body the pathogen was, the less diverse the disease.

The final outcome of an epidemic with two strains

Viggo Andreasen - Roskilde University

Andreasen discussed the outcome of two competing strains of a pathogen when one strain is a resident

strain and the other is an invading mutant. This competition was discussed in the context of an evolutionary game between both strains. The outcome of the competition depends the epidemic properties of each strain (e.g., how virulent each pathogen is), as well as the timing and the size of the outbreak. Traditional deterministic models that take a mean-field approach had difficulties capturing the relative roles that these factors play in the severity of an outbreak. Dr. Andreasen presented a modified mean-field approach that incorporated either full or partial cross-immunity to look at the range of possible outcomes.

The impact of vaccination on Dengue virulence

Jan Medlock –Oregon State University

There are four different groups of Dengue, called serotypes. Dengue has very complex dynamics: which strain is dominant can change from year to year, and there can be complex interactions between serotypes. The modeling framework used by Medlock was based on previous work by Gandon on Malaria vaccines which looked at four potential vaccine actions: slowing pathogen growth, reduction in susceptibility/transmissibility/Dengue pathogenicity. The model is a standard SEIR model with infection possible in both directions between humans and mosquitos. Medlock looked at the impact of vaccination of humans as well as the role that mosquito transgenesis (genetic altering of mosquito) might have on virulence of the pathogen. His model found that vaccines reduce R_0 and result in fewer infections, but can lead to an actual increase in severity (pathogen virulence increases). The results for transgenesis were less clear. Blocking transmission of the pathogen or reducing rate of biting can either increase or decrease virulence, while increasing either background or dengue-induced mortality both serve to decrease virulence.

Thursday

Branching Process Models in Evolutionary Epidemiology

Troy Day -Queen's University

Dr. Day provided a brief overview of multitype branching processes, with particular emphasis on their application in evolutionary epidemiology. He discussed recent work on how such analyses can be used to understand the evolutionary emergence of diseases like pandemic influenza in humans and to evaluate the utility of different interventions. He also discussed how branching processes are being used to understand and control the emergence of drug resistance.

An individual-based approach to adaptive dynamics: a study of evolution and diversification through concentration scalings

Nicolas Champagnat -INRIA Sophia Antipolis

Dr. Champagnat considered a stochastic, individual-based model of an evolving population with logistic density-dependence, where individuals are characterized by a quantitative phenotypic trait. Under appropriate parameters scalings of rare mutations and large populations, he obtained a stochastic jump process on the mutation time-scale, where evolution proceeds through successive invasions of mutants, followed by competition phases on shorter time scales, where disadvantaged traits are eliminated. Under an additional scaling of small mutations and on appropriate time scales, the evolution can be described as ordinary differential equations on the trait space, known as "canonical equations of adaptive dynamics," followed by diversification phases where the number of traits present in the population may increase, a phenomenon known as "evolutionary branching."

Central limit approximations for Markov population processes with countably many types

Malwina Luczak -University of Sheffield

When modeling metapopulation dynamics, the influence of a single patch on the metapopulation depends on the number of individuals in the patch. Since there is usually no obvious natural upper limit on the number of individuals in a patch, this leads to systems in which there are countably infinitely many possible types of entity. Analogous considerations apply in the transmission of parasitic diseases. Dr. Luczak proved central

limit theorems for quite general systems of this kind, together with bounds on the rate of convergence in an appropriately chosen weighted ℓ^1 norm.

A model for the propagation of resistance to a parasite in vectors

Julien Arino -University of Manitoba

One tool envisioned as part of the array of measures used in the fight against malaria takes advantage of a naturally occurring "resistance" of vectors to the parasite. This mechanism results in the disruption of the parasite's life cycle in vectors, rendering the bite of an infected vector harmless because the parasites have not reached the stage where they are infectious to hosts. However, this resistance is not transmitted through regular evolutionary mechanisms and requires the use of so-called transposons. Dr. Arino presented a naive model for the spread of this resistance in a population of vectors.

Life in cells, hosts, and vectors: parasite evolution across scales

Nicole Mideo -University of Edinburgh

Parasite evolution is increasingly being recognized as one of the most important challenges in applied evolutionary biology. Understanding how parasites maximize fitness whilst facing the diverse challenges of living in cells, hosts, and vectors, is central to disease control and offers a novel testing ground for evolutionary theory. Along with Sam Brown, Dr. Mideo recently hosted a symposium to address the question "How do parasites maximize fitness across a range of biological scales?" The symposium brought together researchers whose work looks across scales and environments to understand why and how parasites 'do what they do,' tying together mechanism, evolutionary explanations, and public health implications. Dr. Mideo reported on some of the fascinating research that suggests that understanding the evolution of parasite traits -and the diseases they cause- often requires an appreciation that parasite lives are complex and forces outwith focal host-parasite interactions can shape their traits. Dr. Mideo also highlighted an existing theoretical framework for studying parasite evolution, which provided a useful starting point for embracing this complexity.

Workshop 5: Spatial Models of Micro and Macro Systems

April 16-20, 2012

Organizers: Richard Durrett, Alan Hastings, Steve Krone, and Simon Levin

Report by: Rachel Leander, Jon Lo, and Suzanne Robertson

Monday

Particle systems and reaction diffusion equations: connecting macro and micro models

Steve Krone -University of Idaho

Dr. Krone discussed two types of models used to describe the spatial structure of biological populations: interacting particle systems and reaction diffusion equations. Interacting particle systems are stochastic models that describe local interactions between individuals. In these models, space is discrete while time is continuous. Local interactions are determined by flip dynamics, in which local sites change their type, and exchange dynamics, in which particles move between sites. These two types of dynamics can be combined to produce a related system of reaction-diffusion equations. In particular, the generator of the flip dynamics can be used to convert the interacting particle model into a martingale. Exchange dynamics, meanwhile, are averaged out through scaling, just as a random walk is converted into a Brownian motion. As an example, Dr. Krone introduced a biological system in which multiple species compete for resources. An interacting particle system model of the system exhibits the same qualitative behavior as a reaction-diffusion model of the system, that is, depending on the choice of parameters, the species will die out, coexist in through traveling spiral waves, or coexist with a homogeneous spatial structure. There are, however, subtle differences between the models. In particular, in the reaction-diffusion model, the speed of the traveling wave is proportional to the square root of the growth rate times the diffusion coefficient, while in the particle system, the speed of the traveling wave is proportional to the growth rate. After using both particle system and reaction diffusion models to analyze other example systems, Dr. Krone concluded that by employing both particle system and reaction-diffusion



Alan Hastings

models we enhance our understanding of the underlying biological systems.

Survival and coexistence for a class of stochastic spatial models

Ted Cox -Syracuse University

Dr. Cox discussed a method to analyze the long-term behavior of a class of stochastic models, all of which are perturbations of a well-known model termed the voter model. In these models, individuals are placed on a d-dimensional integer lattice, each individual may be one of two types, and the dynamics of the model are given by a rate function that determines the rate at which each individual changes its type given the current configuration of the system. In analyzing a model's long-term behavior one can consider the probability that a type survives, the probability that a type takes over, or the probability that both types coexist. Dr. Cox noted that the long-term behavior of the voter model is well

defined. In particular, for $d > 2$ there exists a family of stationary distributions that is indexed by the density of ones in the system. Dr. Cox went on to illustrate via example that other models can be viewed as perturbations of the voter model. In order to analyze the long-term behavior of a perturbation of the voter model, a reaction diffusion equation is derived by scaling space and time. Then, the hydrodynamic limit theorem for voter model perturbations is applied. This theorem states that the stochastic process is approximated by the solution of the associated reaction diffusion equation, so that the long-term behavior of the solution to the reaction diffusion equation yields information about the long-term behavior of the stochastic model.

Biological Dispersal Strategies of Internet Worms

David Hiebeler -University of Maine

Dr. Hiebeler began by presenting some background information about offspring dispersal and disease outbreaks in patchy environments. He noted that in general, local crowding favors long-range dispersal, while clustered habitats favor local dispersal. Hence, the most successful dispersal strategy should incorporate a mix of local and long-range dispersal. In the context of a disease epidemic, clustering of suitable habitat may be

the result of vaccination efforts. Dr. Hiebeler's previous analysis of disease models showed that clustering of vaccination within patches increases both the size of the outbreak and the speed with which it spreads.

Dr. Hiebeler went on to describe Internet worms and the mechanisms through which they spread. He noted that a worm, unlike a virus, does not rely on the actions of people to spread. Recent worms propagate via short, medium, and long distance dispersal. In particular, worms may spread via web links, email address book connections, physical connectivity, and IP addresses. As Dr. Hiebeler's research focuses on worms that spread via IP addresses, he explained the IP address system in some detail: An IP address consists of 4 numbers, between 0 and 255. There is not a one-to-one correspondence between machines and addresses. In particular, some machines may share addresses, some machines may have multiple addresses, and some addresses are reserved (i.e. not associated with a machine). Hosts are assigned addresses in a clustered way so that addresses within a university or department are close together.

The first computer worm to use both short- and long-range dispersal was the Code Red II worm, which



Spatial modeling. Auracle Geospatial Science, Inc.'s photostream.

infected more than 100,000 computers in 2001. After infecting a machine the worm would attempt to spread as follows: 37.5% of the time this worm would attempt to infect a computer with an IP address that contained the same first two numbers (short distance dispersal), 50% of the time it would attempt to infect a machine with an IP address with the same first number (medium distance dispersal), and 12.5% of the time it would attempt to infect a computer with a random IP address (long distance dispersal). Previous Internet worms employed long-range dispersal exclusively. All worms since the Code Red II worm employ mixed dispersal strategies.

For the past ten years Dr. Hiebeler has been scanning machines to measure how clustered suitable worm habitats are on the Internet. He used this data to construct a model Internet in order to simulate worm outbreaks. Simulations showed that local dispersal enables worms to spread within a patch while long distance dispersal enables worms to spread to new patches. In particular, his simulations showed that the Internet exhibits enough clustering of suitable habitat to make short distance dispersal advantageous. This clustering of suitable habitat likely results from the IP assignment system. In particular, machines with similar IP addresses are more likely to belong to the same organization and hence to run the same software and to have the same security patches.

Dr. Hiebeler concluded by discussing the future of his research, Internet worms, and the Internet. In particular he noted that future models should incorporate the possibility that a worm is detected, and also consider adaptive dispersal strategies that are being employed by recent worms. Finally, Dr. Hiebeler noted a new larger system of IP addresses is being created. The new Internet will make occupied IP addresses so sparse that long-range dispersal will be obsolete.

First passage time in complex environments: Connecting random walks to functional responses

Mark Lewis -University of Alberta

Dr. Lewis outlined first passage time analysis for animals undertaking complex movement patterns while searching for prey. He extended the analysis to complex heterogeneous environments in order to assess the effects of man-made linear landscape features on functional responses in wolves searching for elk. Dr. Lewis then presented a mechanistic first passage time model, based on an anisotropic elliptic partial differential equation, which he used to explore how wolf movement responses to seismic lines influence the encounter rate of the wolves with their prey.

Tuesday

Stochastic spatio-temporal models confronted with experimental data: invasion, extinction and climate change

Alan Hastings -University of California, Davis

Variability in rates of spread and speeds of biological invasions is expected from inherent demographic, environmental, and genetic stochasticity, yet for natural biological invasions, we usually only observe, and thus have data on, one realization of a stochastic process. Dr. Hastings reported results from a laboratory experiment on the flour beetle *Tribolium castaneum*, in which adults can disperse through boxes of flour connected via small holes. These experiments were maintained for 13 generations of 30 replicates, with new boxes being added to the end of landscapes when needed. The





The role of gene flow in rapid evolutionary response to global change

Marissa Baskett -University of California, Davis

Humans are a major source of environmental heterogeneity in both space and time. Dispersal through heterogeneous environments, and the resulting gene flow between populations, is traditionally believed to hinder the ability of organisms to adapt to local conditions. However, in some cases this genetic exchange may be beneficial, enhancing the adaptive capacity of populations experiencing variable population sizes or environmental shifts. Dr. Baskett presents two models, showing the potential

rate of spread of the beetles was extremely variable, with some cultures dispersing through 30 patches and others only 7. Dr. Hastings developed a mechanistic stochastic model with an individual based derivation in order to predict the mean, variance, and probability distribution of the rates of spread and compare with the data. When comparing models incorporating different types of variation, he found that (for the population model alone) demographic heterogeneity can be mistaken for environmental stochasticity (known to be low for this controlled laboratory system). He also found the risk of extinction to be very sensitive to the type of stochasticity included in the model. He next presented the full spatial model, incorporating an individual Poisson distributed probability of migrating from box y to x . The model predicted variance in distance spread was smaller than observed, and Dr. Hastings found that incorporating Founder effects, and demographic heterogeneity, yielded results with larger variability more closely matching the data. He concluded the talk by discussing application areas of invasive species, range limits, and range shifts under climate change.

for both beneficial and detrimental effects of gene flow under human-driven environmental change. The first is a model of coral adaptation to climate change. Extreme temperatures are an environmental stressor known to cause large-scale bleaching of coral, and climate predictions suggest that without coral adaptation, more frequent mass bleaching events will result in coral extinction by the end of the century. While coral has a long generation time making it unlikely for adaptation to occur, the symbionts responsible for photosynthesis have a shorter generation time, and exhibit variance in thermal tolerance. Dr. Baskett's model for this system predicts that with symbiont diversity, coral adaptation (and survival past the end of the century) may be possible, depending on climate scenarios. She also finds that connectivity between sites has a greater enhancement on the potential for persistence and should be a priority for conservation efforts. Next, Dr. Baskett presented a model of exchange between salmon hatchery and wild salmon populations, looking at the fitness consequences of domestication selection in the hatcheries on the wild population. She found that the relative timing (in the life cycle) of events such as natural selection, density dependence, and release of domesticated

populations, are key to predicting these fitness effects. Both examples presented show how understanding the effects of gene flow can help make decisions for conservation.

Persistence and spatial spread in the face of uncertainty

Sebastian Schreiber -University of California, Davis

The first part of Dr. Schreiber's talk focused on the relationship between attractors of deterministic models and the metastable behavior of discrete models incorporating demographic stochasticity, including results on when persistence should be observed over long time frames despite extinction being inevitable for these models. The second part of the talk focused on how environmental stochasticity influences the persistence of spatial populations and spatial spread, looking at how dispersal interacts with spatial heterogeneity to influence population persistence. For the Acorn Woodpecker, while individual populations may not be able to survive, spatially coupled metapopulations can persist in fluctuating environments, under certain conditions (positive correlation in time and not too high dispersal rate). This provides an example of a situation where a spatially structured population in a stochastic environment can do better than a single population in average conditions. To investigate the effect of environmental stochasticity on spatial spread, Dr. Schreiber next considers integrodifference equations for structured populations with fluctuating environments. He calculates the speed of traveling wave solutions to these models, and looks at the impact of fluctuations in demography and dispersal on these invasion speeds. He finds that demographic variation decreases invasion speed, whereas fluctuations in dispersal rates increase the speed of invasions. Furthermore, positive correlations between dispersal distance and demography can result in even faster invasions. These theoretical findings are illustrated with an application to Perennial Pepperweed.

Post-harvest diseases of apples: from spore dispersal to epidemiology

Rebecca Tyson -University of British Columbia, Okanagan

Fungal infections can cause severe decay of apples during storage in packinghouses, resulting in great economic loss. Spores of this fungus are usually carried by currents from the ground and deposited on fruit, resulting in infection only when the skin of the apple is damaged. While the handling of apples, and orchard

management practices, are believed to have a direct impact on disease incidence of stored fruit, this relationship had not been shown quantitatively. Dr. Tyson found that spore presence predicted very little of collected data on percent apples infected and the severity of infection in packinghouses, and hypothesized this was because spore presence is rare and not enough data was available. To gain insight into this process, Dr. Tyson developed a PDE Gaussian plume model for a point source with the goal of predicting how many spore receptors in an orchard are necessary to obtain an accurate measure of spore presence. She found minimal change in model predictions for more than 4 receptors. She also developed a second model, attempting to make predictions (based on orchard conditions) for how long apples can be stored disease free, since it is very expensive to open storage rooms and check on their status. This second model consisted of a system of ODEs to model the growth of the fungus on a single apple and an SIR-like stochastic process to describe the spread of the fungus between apples. She found that the variability of disease incidence increased with time. If only a 5% economic loss could be tolerated, then the apples should be stored no longer than 7 months.

Evolution of movement behavior and information usage in seasonal environments

Allison Shaw -Princeton University

Many species exhibit long-range migration, including wildebeests, songbirds, salmon, monarchs, and crabs, however migration is usually studied and summarized by taxa, rather than generally. There is need for unifying theoretical models, as many different species migrate, yet migration is usually studied by taxa rather than generally. Also, the reason for migration is not well understood. In this talk, Dr. Shaw seeks to identify general conditions under which animals should migrate. She assumes movement is motivated by growth, survival and reproduction, and occurs in response to spatio-temporal heterogeneity in these resources. She presents a model incorporating landscape variability in seasonality, patch width, and patch quality. Migration is encoded by information usage behavior, where individuals can use information from local resources, historical information (memory, genetic) or social information to drive their movement. She lets optimal movement behavior evolve for different environments, finding that different types of migration can evolve, depending on the ecological

conditions and the availability of information.

Models of cellular migration for cells of different shapes and sizes

Ruth Baker -University of Oxford

The collective motion of cell populations can be described by continuum, partial differential equation models. Different types of motility can be represented by the choice of diffusion coefficient, and cell proliferation by the source terms. Previous models use both linear and nonlinear diffusion terms without a mechanistic justification. In this talk, Dr. Baker presents three models that incorporate individual-level properties of the cell motility mechanism, accounting for varying cell properties such as shape and volume. She presents the corresponding population-level partial differential equation formulation for each of the individual sites, stretched lattice and individual agents models, obtaining a nonlinear degenerate diffusion coefficient, linear diffusion coefficient, and nonlinear non-degenerate diffusion coefficient, respectively. With no cell proliferation, these three models all perform well at predicting the population-level response of a cell-spreading problem. In the case with proliferation, there is greater variation in performance, with the individual agents model the clear best choice. The potential of these models to predict long time travelling wave invasion rates is also discussed.



can separate and recover original groups as well as admixed individuals, with a threshold behavior (in number of SNPs or markers) present for the detection of population structure. Dr. Novembre considers the case of spatially structured, or isolated by distance, populations. He finds that for 2-d spatial habitats, PCA results match the basis of the discrete cosine transform – a gradient for PC 1, perpendicular gradient for PC 2, saddle for PC 3 and mound for PC 4. This is a generic consequence of spatial data depending on the size and shape of the domain rather than a specific indicator of population expansion. In fact, experiments with bacteria indicate a population expansion would occur perpendicular to the gradient in PC 1. However, for distance isolated populations, PCA does behave as if we put spatial position as a covariate in association mapping models. PC 1 and PC 2 can be used as latitude and longitude to produce a map-like representation of populations with genetic data alone and spatial predictions as to individual ancestry can be made. Dr. Novembre concluded his talk by discussing model-based approaches for spatial genetic approaches, along with their associated challenges and potential directions. He presented 2 applications – inference using Fisher's wave of advance model, and spatial assignment applications using data from migratory birds.

Wednesday

Influence of migration and dispersal in spatial population genetic models

John Novembre -University of California, LA

Dr. Novembre uses theoretical models and statistical inference to link observed genetic diversity data to inferred evolutionary processes, such as human population history and individual ancestry. Principle component analysis has been used to summarize genetic variation and make inferences, with populations as the units of analysis and allele frequencies as multivariate observations. For discrete groups of populations, PCA



Mercedes Pascual

Experimental ecology and evolution in metapopulations

Ben Kerr -University of Washington

Dr. Kerr spoke about the ways in which population structure can affect ecological and evolutionary dynamics. In particular, he discussed two examples.

The first example involved a strain of bacteria that can produce antimicrobial proteins. Under stress a small fraction of these bacteria release toxins into the medium via lysis, bacteria that are unable to produce the toxin are susceptible to its effects, hence these bacteria are killed on uptake of the toxin, latent producers, on the other hand, are immune to the toxin. In addition, sensitive cells can give rise to resistant cells via mutation. These bacteria exhibit a non-transitive relationship, that is, sensitive cells outgrow resistant cells, resistant cells outgrow toxin producers, and toxin producers kill sensitive cells. Mathematical analysis predicted and experimental results confirmed that although all three

players cannot coexist in a well-mixed community, in a structured community, coexistence is possible. In the course of performing experiments with the system Dr. Kerr's group noted that mutations arose in the resistant strain. A system of differential equations was used to explore this phenomenon. Interestingly they found that under well-mixed conditions, mutations that increase a strain's replacement rate decrease its density, hence a strain can "improve itself to death." In a structured community, meanwhile, the model showed that aggressive strains die out, while less aggressive strains can persist. Dr. Kerr's group tested the model's predictions experimentally. Experiments confirmed that structured populations promote the evolution of restraint.

The second example involved a phage (viral parasite) of *E. coli*. Under experimental conditions bacteria and phages do not coexist in a single well. Dilutions and migrations between wells results in a non-transitive

system in which bacteria replace an empty well, phages replace bacteria, and empty wells replace phage filled wells. Dilution and migration experiments were performed and the dynamics were described via a non-linear Markov chain. At low migration rates the model predicts that the virus goes extinct. As the migration rate increases the model predicts that the phage and bacteria will coexist, at first through a fixed point and then through a stable cycle. In addition, numerical simulations predict that under restricted migration phage density will be lower, while ecological dynamics will be more stable. Experimental results agreed with each of these predictions with the exception of the final prediction that restricted migration will lower phage density. Kerr's group measured phage productivity, and competitive ability to see if the discrepancy between the model's predictions and the experimental results could be the result of evolution. They discovered that during the course of the experiment phages subject to unrestricted migration became less productive but more competitive, that is, they followed a live fast die young strategy, while phages subject to restricted migration became less competitive, more productive, and less virulent.

Go forth and multiply

Steven Evans -University of California, Berkeley

An individual's survivorship and fecundity depend on environmental conditions that vary in space and time. Individuals can modulate their fitness through offspring dispersal. Researchers have used various modeling frameworks to analyze how dispersal can influence population persistence in heterogeneous environment. In particular, for models of population growth in which time is discrete and the fitness of a location varies there are situations in which every local population would go extinct in the absence of dispersal while every local population would persist in the presence of dispersal. In this talk Dr. Evans discussed what we can be said about persistence in continuous time stochastic models with temporal variations in the fitness of locations. After deriving a continuous time stochastic model Dr. Evans explained how one estimates the population's long-term exponential growth rate. For a simple two-patch model he showed that increasing the dispersal rate enables a population that would otherwise go extinct to persist. Dr. Evans went on to discuss a model in which the environmental conditions are fixed. For this model

Dr. Evans showed that individuals maximize the population's long-term exponential growth rate by dispersing as quickly as possible. For a specific realization of this model he also showed that ideal free dispersers visit all patches provided the environmental variation is sufficiently great relative to the difference in the per-capita growth rates. Finally Dr. Evans discussed what happens to the exponential growth rate as the rate of dispersal decreases for more general models.

Thursday

Collective motion and collective decision-making

Simon Levin -Princeton University

Dr. Levin discussed about some models of animal aggregation and the role of leadership in collective motion. He introduced a brief history of research on the mathematical modeling of animal populations, largely built on diffusion models. It included pattern formation in non-convex or convex regions, and Turing pattern with drastic differences of diffusion coefficients among species. He pointed out that the classical literature is inadequate to explain observed spatial patterning, or foraging and anti-predator behavior, because animals actively aggregate. He and his collaborators proposed several models of animal aggregation, and collective motion. By studying the role of leadership in collective motion, he concluded that leadership and following can coexist and leader is providing a public good. Also, multiple outcomes are possible in the presence of conflicting leader opinions and unopinionated individuals can enhance consensus in favor of the majority opinion.

Forest fires, cholera epidemics and spatial stochastic systems with critical transitions

Mercedes Pascual -University of Michigan

Dr. Pascual first introduced a simple forest fire model - Drossel Schewabl model (DSM) and briefly discussed a data of the patterns in the epidemic dynamics of measles. The recent data of wildfire size distributions provide more information to modify DSM to predict the patterns and the dynamics of wildfire more accurately. The extended DSM provides an explanation for the heavy-tailed, power-law like distributions of event sizes, which are observed in the recent data of wildfire size distributions. There are several evidences that cholera epidemics have similar patterns with wildfire. She applied forest fire model to explain disease dynamics and

classify epidemic dynamics into subcritical and supercritical behavior; this indicates which mechanism controls epidemic size.

Secondary characteristics of spatially and temporally heterogeneous populations

Daniel Grunbaum -University of Washington, Seattle

Dr. Grunbaum first pointed out that most ecological interactions occur in environments that are spatially and temporally heterogeneous, 'patchy', across a wide range of scales. In contrast, most theoretical models of ecological interactions, especially large-scale models applied to societal issues such as climate change, resource management and human health, are based on 'mean field' approaches in which the underlying patchiness of interacting consumers and resources is intentionally averaged out. Then he discussed about large-scale characteristics of interacting populations in which spatial and temporal heterogeneity is either imposed by external environmental forcing or arises autonomously from social interactions such as schooling and swarming. In many such populations, secondary population characteristics emerge that operate over larger spatio-temporal scales than primary patch dynamics and that strongly affect ecological outcomes. He introduced some examples in which analysis of these secondary characteristics may improve interpretation and prediction of unresolved patch dynamics in data and models.

Evolution of dispersal and the ideal free distribution

Steve Cantrell -University of Miami

Dr. Cantrell first proposed a question in the study of the evolution of dispersal, "Can dispersal evolve in habitats that are spatially heterogeneous but temporally constant, and if so, what dispersal strategies are likely to evolve?" He considered a two species competition model in which the species are assumed to have the same population dynamics but different dispersal strategies. Both species disperse by random diffusion and advection along certain gradients, with the same random dispersal rates but different advection coefficients. The analysis showed a conditional dispersal strategy which results in the ideal free distribution of species, and showed that it is a locally evolutionarily stable strategy. The results further showed that this strategy is also a globally convergent stable strategy under suitable assumptions, and illustrated how the evolution of dispersal can lead to an ideal free distribution. The underlying

biological reason is that the species with this particular dispersal strategy can perfectly match the environmental resource, which leads to its fitness being equilibrated across the habitat.

Voter model perturbations and the evolution of the dispersal distance

Daniel Remenik -University of Toronto

Dr. Remenik considered the problem of choice of seed size for plants in a stable environment when there is a trade off between survivability and dispersal range. He introduced a stochastic spatial model to study the competition of different strategies. The results were obtained by simulation or non-rigorous methods such as pair approximation. The work was based on a model of the general voter model perturbations recently studied by Cox, Durrett, and Perkins (2011) that allows him to rigorously and explicitly compute evolutionarily stable strategies. He extended the earlier work to three- or higher dimensional cases and the more complicated two-dimensional case, and discussed the difference of the results in all the cases he considered.

Weak and Slow: Spatial patterns in a heterogeneous environment

Bard Ermentrout -University of Pittsburgh

Dr. Ermentrout considered the interactions between heterogeneities and delayed negative feedback in systems that admit stationary persistent structures. The former can cause pinning and stabilize neutrally stable dynamics while the latter can induce several types of dynamics instabilities and motion. He showed that the time-scale of the negative feedback and the amplitude of the heterogeneities interact to produce qualitatively different sequences of bifurcations. The models are motivated by dynamics of neurons in the rodent hippocampus during navigation.

Friday

Two-strategy games on the lattice

Nicolas Lanchier -Arizona State University

Dr. Lanchier's work is at the origin of the popular framework of evolutionary game theory. Space is another component that has been identified as a key factor in how communities are shaped. Spatial game models are therefore of primary interest for biologists and sociologists. In this talk, he discussed the difference between



Simon Levin

spatial game on the lattice and non-spatial deterministic game. The objective of this talk is to explore the framework analytically through a simple spatial game model based on interacting particle systems (agent-based models). Their results indicate that the behavior of this process strongly differs from the one of its non-spatial mean-field approximation, which reveals the importance of space in game theoretic interactions.

Evolving voter model

Rick Durrett -Duke University

Dr. Durrett first introduced Holme and Newman voter model and its properties. In the evolving voter model, we choose oriented edges (x,y) at random. If the two individuals have the same opinion, nothing happens. Otherwise, with probability $1-\alpha$, x imitates y , and with probability α , x severs the connection with y and picks a new neighbor at random from those with the same opinion as x . The study showed that α controls the size of the opinion components. Later, He based on the

Holme and Newman model to build up a voter model with continuous time. In this model, events happen on each oriented edges (x,y) at times of a rate one Poisson process. For the case with probability α , x severs the connection with y and picks a new neighbor at random (i) from the graph, or (ii) from those with the same opinion as x . Despite the similarity of the rules, the two versions have much different phase transitions. This difference can be traced to differences in the arch of quasi-stationary distributions.

Workshop 6: Algebraic Methods in Systems and Evolutionary Biology

May 7-11, 2012

Organizers: Reinhard Laubenbacher, Ilya Shmulevich, Seth Sullivan, and Ruriko Yoshida

Report by: Marisa Eisenberg, Sam Handelman, and Franziska Hinkelmann

Monday

Autonomous Boolean network modeling of gene regulation in early embryonic development

Joshua Socolar- Duke University

Dr. Socolar introduced a Boolean network formalism that allows for modeling time delays inherent to gene regulatory processes, autonomous Boolean networks with continuous time. Boolean models with continuous-time updates can directly represent timing information that determines the dynamics of a gene regulatory network. He described the relation between autonomous Boolean models and differential equation models, emphasizing the advantages of the Boolean approach for certain system types. He applied his approach to an experimentally well-studied example of the gene network that controls fly body segmentation in *Drosophila*. An autonomous Boolean model successfully recapitulates the patterns formed in normal and genetically perturbed fly embryos and permits the derivation of constraints on the time delay parameters for the formation of experimentally observed patterns. The Boolean model captures the essential features of previously presented differential equation models and clarifies the logic associated with different parameter choices.

Phylogenetic trees of regulatory networks

Ruriko Yoshida- University of Kentucky

Dr. Yoshida gave an introductory talk on inferring networks using phylogenetic trees. Consider the case of inferring a gene regulatory/coexpression/metabolic network from biological data in a given species. Recent studies have shown that these networks have many interesting dynamic features such as mutational robustness and evolvability. Every network in a particular species has an associated evolutionary history. Evolution can modify a gene network using mechanisms such as

gene duplication, horizontal gene transfer, and neofunctionalization. In addition, sequence evolution can act on individual genes as well as their promoter regions. Thus comparative and evolutionary information may help improve the accuracy of inferred biological networks in individual species. She proposed to use Graphical Gaussian model and Graphical Lasso for inference on an ancestral network.

Criticality in genetic networks is an emergent property in evolution

Maximino Aldana- Universidad Nacional Autonoma de Mexico

Dr. Aldana's talk showed that critical dynamics in genetic network models naturally emerge as a robust byproduct of the very same evolutionary processes that select for evolvability – without fine-tuning of parameters or imposing explicit selection criteria (i.e. arbitrary fitness functions). Gene regulatory networks that operate in the dynamically critical regime (between order and chaos) are optimized with respect to the trade-off between phenotypic robustness and flexibility - a balance that ensures both homeostasis and development. In fact analyses of the gene network architecture and patterns of transcriptome changes in several organisms in the past few years suggest that the gene regulatory networks of living organisms are indeed in the critical regime. But how does a gene regulatory network evolve a structure that confers criticality? While this question has evaded scientists for decades, a related equally fundamental question has over the past years attracted considerable interest: The evolution of evolvability. There is now the consensus that evolvability itself is a selectable trait. Evolvability, similar to criticality, is associated with the trade-off between mutational robustness on the one hand (mutations should not disrupt essential functions) and innovation on the other hand (mutations should alter networks sufficiently to add new functions).



Panel discussion

Criticality emerges from the requirement of evolvability in the sense that during evolution, the existing adaptive phenotypes must be preserved while allowing new phenotypes to emerge for the organism to be able to cope with new environmental challenges. Strikingly, the gene networks produced by selecting for evolvability have a structure (topology) that is very similar to the one observed in real organisms, such as *Escherichia coli*, characterized by the existence of global regulators.

Boolean versus continuous dynamics on gene regulatory networks

Eva Christina Ackermann- TU Darmstadt

Dr. Ackermann studies the relationship between continuous and Boolean dynamics of gene regulatory networks, by using simple modules as well as complex networks.

She showed how a Boolean model for gene activity can be translated into continuous dynamics for mRNA and protein concentrations using sigmoidal Hill functions and established conditions under which dynamical attractors of the Boolean and the continuous model agree with each other. These conditions depend only on general features such as the ratio of the relevant time scales, the degree of cooperativity of the regulating interactions, the logical structure of the interactions, and the robustness of the dynamical patterns under random time delay.

Algebraic Theory for Discrete Models in Systems Biology

Franziska Hinkelmann- Mathematical Biosciences Institute

Dr. Hinkelmann's talk introduced an algebraic framework, namely polynomial dynamical systems, for



discrete models and explained how she and her collaborators used it to identify potential therapeutic targets in human Melanoma cells. Experimental evidence suggests that retinoic acid (RA) deactivates the canonical Wnt signaling pathway in early stage melanoma cells. More aggressive melanoma cell lines are not responsive to RA. Using a systems biology approach, a mathematical model was constructed of the canonical Wnt signaling pathway and the PCP pathway, including their cross-talk, to investigate which proteins have the ability to reduce the cell growth rate in the more aggressive vertical growth phase (WM1366) cells. Model analysis identified LRP6 as a target that might inhibit cell growth. Experimental verification of this hypothesis showed that down-regulation of LRP6 greatly reduced the growth rate, thus providing a potential target for therapy of this tumor type. The model used is a polynomial dynamical system (PDS), that is, time- and state-discrete dynamical systems over a finite field where the transition function for each variable is given as a polynomial. This allows for using a range of theoretical and computational tools from computer algebra, which results in a powerful computational engine for model construction, parameter estimation, and analysis methods.

Tuesday

Avenues toward simplified Boolean modeling of signal transduction networks

Reka Albert- Pennsylvania State University

Dr. Albert discussed her work developing methods for simplifying and analyzing Boolean models for signal transduction networks. She began by introducing the terminology and three case study models of abscisic acid induced closure of plant stomata, respiratory infection in mice, and survival of cytotoxic T-cells in T-LGL leukemia. She next discussed some of the difficulties with analyzing larger Boolean models, due to combinatorial explosion of the state space as one adds nodes. Based on this, a question of interest is: how to simplify a given network with minimal effect on the dynamics? Dr. Albert examined several approaches to network reduction, which can drastically reduce the number of variables without affecting the network dynamics. Next she discussed the ambiguities of how to implement time for Boolean network models, given that different processes may have different, unknown timescales. She presented a comparative analysis of several asynchronous update methods and showed that updating a single, randomly selected node at each time instant offers the best combination of information and economy. Lastly, she

discussed an integration of Boolean rules into graph theoretical analysis and showed that this semi-structural method can identify critical signal mediators on par with dynamic models.

Cancer Therapy Design Based on Pathway Logic

Aniruddha Datta- Texas A & M University

Dr. Datta discussed his work using an engineering and pathway logic-based approach to modeling cancer. He began with an overview of the cancer biology and microarray data approach used for examining cancer signaling pathways, and discussed how cancer is usually caused by malfunctions in the cellular signaling pathways. He discussed how examining the locations and effects of stuck-at faults in Boolean circuit models of cancer can give insight into effective drug combinations that might be able to return a dys-regulated system back to a normal state. He considered growth factor signaling pathways, widely studied in the context of cancer, with interactions between different pathway components modeled using Boolean logic gates. He presented a method of output analysis where all possible single malfunctions in the resulting circuit are enumerated and responses of the different malfunctioning circuits to a 'test' input are used to group the malfunctions into classes. Using this approach, effects of different drugs targeting different parts of the Boolean circuit can be taken into account in deciding drug efficacy, thereby mapping each malfunction to an appropriate set of drugs. This allows the modeler to develop a systematic look-up table to predict the best possible drug combination to counteract the effect of a single stuck-at fault.

Linking the Signaling Cascades and Dynamic Regulatory Networks Controlling Cellular Responses

Ziv Bar-Joseph- Carnegie Mellon University

Dr. Bar-Joseph began with a computational sidenote on how biology may be able to contribute to solving computer science questions, as many exciting research directions in computer science share principles in biology, e.g., stochasticity (for dealing with NP problems), modularity, and network processes. In the spirit of this exchange between computation and biology, Dr. Bar-Joseph then switched the focus to larger scale models of transcriptional gene regulation. He discussed how to upgrade static biological data (e.g., sequence data) using time-course data and models to yield time-course information. By combining the abundant static regula-

tory data with time series expression data using an Input-Output Hidden Markov model (IOHMM), they were able to reconstruct dynamic representations for these networks in multiple species. These models lead to testable temporal hypotheses identifying both new regulators and their time of activation. Dr. Bar-Joseph also discussed their recent extension of these models to connect signaling and regulatory networks. Their work involves solving an optimization problem related to graph orientation, and the resulting reconstructed networks link receptors and proteins that directly interact with the environment to the observed expression outcome. He discussed several applications and experimental validation of predictions made by these methods for the yeast stress response. Lastly, he finished his talk by discussing several open problems that remain in this area, including incorporating microRNAs, discovering combinatorial regulation, and dealing with feedback.

Non-parametric analysis of mass action models and data

Heather Harrington- Imperial College London

Dr. Harrington discussed using steady-state invariants for model selection in mass-action models. She discussed how cell decision-making mechanisms are quite complex, so that it is often possible to build many different plausible models. She presented an algebraic geometry-based method using Gröbner bases to determine steady state invariants. Using this approach, she developed a coplanarity-based test of whether a model is compatible with a given set of steady state data. This framework was developed for the best-case, noiseless data scenario, so to examine realistic cases where the data is noisy, she developed a coplanarity error measure that allows one to reject the model if the coplanarity error is too large. Next, she showed several examples using multisite phosphorylation where it was possible to reject some of the models, although in other cases this is not possible (if the invariants for one model can be made to match the invariants for another model, e.g. by setting coefficients to zero). She also showed that cellular information processing can be altered by including spatial organization. Using tools from chemical reaction network theory and dynamical systems, she showed that the existence of distinct compartments can alter whether a system is capable of multistationarity.



Invariants - polynomial signatures of molecular networks

Jeremy Gunawardena- Systems Biology, Harvard Medical School

Dr. Gunawardena discussed using steady state invariants to examine the molecular networks using mass action models. He began with some background information on chemical reaction networks and discussed how steady state information can be useful, and how examining the steady state signature of a model can help to rise above some of the complexity issues that come with molecular biology. A network of biochemical reactions using mass-action kinetics forms a polynomial dynamical system, the steady states of which form a real algebraic variety. Using techniques from computational algebraic geometry, Dr. Gunawardena has developed methods for connecting models with steady state data using invariants (polynomial expressions in specified state variables that hold in any (positive) steady state of a network). Dr. Gunawardena discussed how looking at chemical reaction network models in steady state allows one to drastically reduce the complexity of the model, using algebraic relations among the variables. He discussed how this approach could give insights into chemical reaction network properties, for example examining the relationship between reversibility and ultrasensitivity. While invariants characterize the behavior of several model networks and concisely capture their salient behavior, calculating them can be computational-

ly infeasible (particularly using Gröbner bases). Dr. Gunawardena next presented an approach to generating invariants using chemical reaction network theory which is significantly faster but may not generate complete set of invariants (as it restricts to using the complex monomials to generate invariants).

Wednesday

Coloured Petri Nets for Multiscale Systems Biology **Monika Heiner- Brandenburg University of Technology at Cottbus**

Dr. Heiner discussed using Petri nets for modeling in systems biology. Petri nets have a structure that emphasizes interactions, naturally lending itself to modeling systems biology. They also have the advantage that they are generally quite flexible in how they are implemented, so that the same petri net can be converted between qualitative, stochastic, and continuous time domains as needed. She explored several examples of models, including glycolysis and the pentose phosphate pathway, apoptosis in mammalian cells, and the lac operon. Dr. Heiner discussed how to reduce networks and analyze their properties, for example to test if they are live and bounded. She also discussed some of the tools her group has developed for building and analyzing Petri net models. Lastly, she discussed an extension of the Petri net framework, called colored Petri nets, which allows the modeler to adjust the scale and level of detail to build larger Petri net models that can be “folded in” to smaller models so that computational complexity is kept small even though very large models can be considered. She began with an ecological example in which one might have multiple predators and prey interacting with one another, but with similar underlying dynamics. By taking advantage of this repeated structure, she can assign a color to each predator prey pair and simplify the model significantly. This colored Petri net framework can also be applied to model multiple receptor types, or even to do diffusion simulations with a scalable grid size. She finished her talk with an example using planar cell polarity in *Drosophila* wings, where she used a colored Petri net approach to build a model that matched experiments, identifying patches of mutated hairs amongst the wild-type hairs of the wing.

*Transcriptional Regulatory Networks from the Bottom Down***Ilya Shmulevich- Institute for Systems Biology**

Dr. Shmulevich discussed how biological systems can be viewed in terms of biological circuits, with modules, emergent properties, crosstalk, and feedback. Biological systems often exhibit properties that come from the interactions of their parts rather than from any single part alone (there are many examples of this in pattern formation, oscillating systems, etc.). Additionally, biological systems must maintain a nonequilibrium steady state in the face of changing conditions, which leads to a tradeoff between adaptability and stability, which ties in to the notion of criticality. Critical systems are often associated with systems having power law-type behavior with no characteristic scale, which shows up in many natural phenomena (e.g., earthquakes, finance, and brain dynamics). In this talk, Dr. Shmulevich examined Boolean networks and criticality. He examined critical phase transitions in Boolean systems where the transition from order to criticality to chaos is marked by a particular curve. Using a Kolmogorov complexity-based measure of informational distance, he examined issues of criticality, stability, and responsiveness in a wide range of systems, including macrophages and immune response, and oleate and galactose metabolism in yeast. To examine the stability and adaptability of systems he also used a frequency based approach using a Fourier transforms taken over sliding short time windows. This allows the responsiveness to different frequency inputs to be examined over time, to see how input output relationships change as the network topology is perturbed. These different approaches provide promising frameworks for studying fundamental principles governing living systems at all scales of organization. Criticality, in particular, seems to be a key property of biological systems to avoid information loss over time.

*Intrinsically Bayesian Robust Structural Intervention and the Mean Objective Cost of Uncertainty in Gene Regulatory Networks***Edward R. Dougherty- Texas A&M University, Translational Genomics Research Institute**

Dr. Dougherty asks: what is the mathematical foundation of classifiers for small samples? And, how can gene networks be used to design interventions? In both cases, significant uncertainty in the underlying network or feature labels is a significant confounder. The

question then becomes, how do we identify a robust intervention across the uncertainty in the network or labels? Dr. Dougherty emphasized the antiquity of these questions in control theory using different filtering methods, with developments from the 1950s to the present. Dr. Dougherty's approach reduces the outlier-sensitivity of these methods, and which concentrates on the objectives of these interventions, and the impact of uncertainty on the model on the ability to achieve these objectives. Dr. Dougherty emphasized the advantages of analytical rather than simulation approaches in the context of control theory in the presence of such uncertainty, with examples from practical applications to cell networks in cancer.

Thursday*Persistence, permanence, and global stability of dynamical systems derived from biological interaction networks***Gheorghe Craciun- University of Wisconsin-Madison**

Dynamical system models are very commonly used to analyze biological interaction networks, such as the dynamics of concentrations in biochemical reaction networks, the spread of infectious diseases within a population, and the dynamics of species in an ecosystem. Persistence and permanence are properties of dynamical systems that provide information about the long-term behavior of the system. For example, the persistence property is relevant in deciding if, in the long term, a chemical species will be completely consumed by a reaction network, an infection will die off, or a species in an ecosystem will become extinct. Dr. Craciun showed that two-species mass-action systems derived from weakly reversible networks are both persistent and permanent, for any values of the reaction rate parameters. Moreover, a larger class of networks, called endotactic networks, also gives rise to persistent systems, even if we allow the reaction rate parameters to vary in time. The results Dr. Craciun presented also apply to general polynomial dynamical systems and other non-linear dynamical systems.

*An Algebra-Based Method to Infer the Structure and Dynamics of Gene Regulatory Networks***Paola Vera-Licona- Institut Curie, Paris**

Dr. Vera-Licona sought to reconstruct, reverse-engineer, or infer a dynamic regulatory network from high-throughput data, especially transcriptomics measure-

ments. She described an iterative approach in which the network is repeatedly checked against the observations. It is desirable for such a method to capture the dynamics of the network under perturbations, and because the model is under determined, there are major advantages to incorporating other biological information. In the context of a boolean polynomial dynamical system, Dr. Vera-Licona combined discretized time-series measurements of the states of the nodes and a biologically derived interaction matrix of prior estimates of interaction probabilities. The states are fit to polynomials and evolutionary methods are combined with algebraic methods to search the space of possible models, allowing for some errors in the states (binomial variables corresponding to the individual nodes). Dr. Vera-Licona provided validation examples showing the good efficiency and power of her approach.

A stochastic model for the evolution of metabolic network using neighbor dependence

Aziz Mithani- LUMS School of Science and Engineering

Dr. Mithani tackled a problem of immense theoretical interest and practical import: how the evolutionary relationship among metabolic networks can be inferred when only the genomes of the organisms are known. Dr. Mithani began by describing metabolic networks and their graph representations, and how evolution between these networks can be described. Dr. Mithani's approach assumes that evolution of these networks proceeds as a Markovian process where hyperedges connecting multiple reactants and products (equivalent to the gain or loss of an enzyme with the corresponding substrates) are gained or lost. These networks are amenable to conventional maximum likelihood reconstruction on phylogenetic trees. The parameters of the network evolution are then estimated using a Gibbs' sampler. The samplers are used to estimate the parameters of evolution of metabolic networks of bacteria in the genus *Pseudomonas* and to infer the metabolic networks of the ancestral pseudomonads. The results suggest that pathway maps that are conserved across the *Pseudomonas* phylogeny have a stronger neighborhood structure than those which have a variable distribution of reactions across the phylogeny, and that some *Pseudomonas* lineages are going through genome reduction resulting in the loss of a number of reactions from their metabolic networks.

Reverse Engineering of Regulatory Networks Using Algebraic Geometry

Alan Veliz-Cuba- University of Nebraska-Lincoln

Dr. Veliz-Cuba used a geometric approach to reverse-engineer a regulatory network from transcriptomic data. Dr. Veliz-Cuba's approach concentrates on identifying minimal wiring diagrams (regulatory networks) that are compatible with the observed data. This has advantages analogous to parsimonious approaches in other fields (such as LASSO) when only partial information is available and/or when the model is seriously under-determined. Dr. Veliz-Cuba's approach achieves this using ideals of polynomials to represent the space of possible regulatory networks, and identifies minimal/parsimonious networks using the primary decomposition of that ideal.

Logical modelling of regulatory networks, results and challenges

Elisabeth Remy- Institut de Mathématiques de Luminy

Dr. Remy discussed logical methods as applied to two classes of graphs relevant to describing biological systems; a regulatory graph with edges representing interactions between genes and a state-graph with edges representing transmission probabilities between states. Building on a running theme of the workshop, prior biological knowledge can be incorporated into both graphs. The dynamics of the state-graph can be predicted using logical methods from local topological features of the regulatory graph. Dr. Remy provides a summary of the relevant fields with questions from the audience and goes over application examples. Dr. Remy's method performs well on both apoptosis and cell-cycle regulatory examples.

Friday

Optimality of the Neighbor Joining Algorithm and Faces of the Balanced Minimum Evolution Polytope

David Haws- University of Kentucky

Dr. Haws talked about phylogenetic reconstruction. Balanced minimum evolution (BME) is a statistically consistent distance-based method to reconstruct a phylogenetic tree from an alignment of molecular data. In 2000, Pauplin showed that the BME method is equivalent to optimizing a linear functional over the BME polytope, the convex hull of the BME vectors obtained from Pauplin's formula applied to all binary trees. The

BME method is related to the popular Neighbor Joining (NJ) algorithm, now known to be a greedy optimization of the BME principle. He elucidated some of the structure of the BME polytope and strengthened the connection between the BME method and NJ Algorithm. Any subtree-prune-regraft move from a binary tree to another binary tree corresponds to an edge of the BME polytope.

Chemical reaction systems with toric steady states

Anne Shiu- University of Chicago

Dr. Shiu works on algebraic methods for analyzing chemical reaction networks. Chemical reaction networks taken with mass-action kinetics are dynamical systems governed by polynomial differential equations that arise in systems biology. In general, establishing the existence of (multiple) steady states is challenging, as it requires the solution of a large system of polynomials with unknown coefficients. If, however, the steady state ideal of the system is a binomial ideal, then she showed that these questions could be answered easily. In her talk, she focused on systems with this property, which have toric steady states. Her main result in this talk gave sufficient conditions for a chemical reaction system to admit toric steady states. She also talked about analyzing the capacity of such a system to exhibit multiple steady states. An important application concerns the biochemical reaction networks that describe the multisite phosphorylation of a protein by a kinase/phosphatase pair in a sequential and distributive mechanism. No prior knowledge of chemical reaction network theory or binomial ideals will be assumed.

Algebraic methods in systems and evolutionary biology

Reinhard Laubenbacher- Virginia Tech

Dr. Laubenbacher concluded the meeting with a review of the workshop, a synthesis of the topics discussed and a distillation of some central themes that point to opportunities and challenges in the field. For Dr. Laubenbacher, this workshop was motivated by “A decade of algebraic methods in biology,” including:

- Reverse engineering of networks using computer algebra over finite fields;
- Analysis of biochemical reaction networks using algebraic structure;
- Evolutionary biology and algebraic statistics.

The goal was to find a common theme among these, and the underlying idea was to have a workshop on “Evolution of Networks.” He categorized the talks roughly into the following categories:

- Different frameworks;
- Technical advances;
- Network inference;
- Comparison of frameworks;
- Evolution of networks.

Dr. Laubenbacher concluded with pointing out challenges and future directions of the field.



Workshop for Young Researchers in Mathematical Biology

August 29 - September 1, 2011

Organizers: MBI Postdocs

Report by: Casey Diekman and Marisa Eisenberg

Monday

Challenges for computational vision: From random dots to the wagon wheel illusion

Leon Glass -McGill University

The first speaker used two visual illusions—Glass patterns in randomly placed dots and the wagon wheel illusion to explore connections between visual processing in the brain, how we perceive correlation, and bifurcations and nonlinear dynamics. For the first half of his talk, Professor Glass introduced and demonstrated Glass patterns, which are formed by overlaying two copies of a random pattern of dots and shifting them slightly from one another. Based on the type of transformation applied to the overlaying dots, the brain perceives different patterns in the overlaid dots, which correspond to vector field diagrams for common dynamical systems patterns—Prof. Glass showed patterns for saddles, ellipses (periodic orbits), spirals, etc. Interestingly, if one views only a small portion of the overlaid dots, these patterns aren't apparent—he found that somehow the brain is integrating numerous local cues to produce a global pattern. Glass proposed a model of visual processing based on autocorrelation that would explain our perception of Glass patterns. In the second half of his talk, Prof. Glass discussed the wagon wheel illusion, in which a rotating disk with radial spokes is viewed under stroboscopic illumination, and the frequency and duration of the stroboscopic flash are varied. This effect is often seen in car advertisements and movies, due to the aliasing of the rotation with the scan rate of the movie. Though these phenomena are very different, both correlations play a major role in defining the structure of the image. Prof. Glass discussed some recent work using the theory of forced nonlinear oscillations to predict the percept of rotating disks dur-

ing stroboscopic illumination over a wide range of disk rotation speeds and strobe frequencies.

A three-dimensional computational model of necrotizing enterocolitis

Jared Barber -University of Pittsburgh

The second session opened with a talk by Jared Barber on modeling necrotizing enterocolitis. Necrotizing enterocolitis (NEC) is a severe inflammatory disease in premature infants that is characterized by wounds in the intestinal wall, which can cause death, developmental delays due to malabsorption, and short bowel syndrome. The ongoing dynamics of the disease depend upon a complex interplay between the immune system, intestinal bacteria, and intestinal epithelium. Dr. Barber has developed one of the first spatial models of NEC, using four layers—lumen, epithelial, tissue, and blood. They used this three-dimensional computational model to examine how wound healing in NEC depends on the spatial structure of the intestine. Using this model, they were able to reproduce physiologically realistic results and show that the spatial structure of intestinal wounds may affect the outcome of necrotizing enterocolitis.

Steady-state invariant genetics: probing the role of morphogen gradient dynamics in developmental patterning

Marcos Nahmad -CALTECH

Next, Marcos Nahmad explored embryonic pattern formation, looking at how cells acquire information about their position and identity within a developing embryo. He is particularly interested in how the dynamics of gradients affects cell fate decisions. The problem of whether or not morphogen gradient dynamics contribute to developmental patterning has not been explored in detail, in part, because genetic experiments that selectively affect signaling dynamics while maintaining unchanged the steady-state morphogen profile are difficult to design and interpret. Nahmad presented a



Participants in the Workshop for Young Researchers on Mathematical Biology.



Leon Glass

mathematical approach to identify genetic mutations in developmental patterning that may affect the transient, but leave invariant the steady-state signalling gradient. He examined what types of perturbations form steady state invariant perturbations, using Hedgehog signaling as a case study in fruit fly development. Using this example, he showed how this method can be used to design experiments to probe the role of transient morphogen gradients in developmental patterning.

Computational explorations of cellular blebbing

Wanda Strychalski -University of California, Davis

In the last talk of the morning, Wanda Strychalski discussed modeling cellular blebbing. Blebbing occurs when the cytoskeleton detaches from the cell membrane, resulting in the pressure-driven flow of cytosol towards the area of detachment and the local expansion of the cell membrane. Blebbing motility is used by cancer cells to migrate through three dimensional matrix. Strychalski gave an overview of previous models, and then introduced a dynamic computational model of the cell that includes mechanics of and the interactions between the intracellular fluid, the actin cortex, and the cell membrane. The model parameters were

partly determined from the literature, and fit the rest to best match experimental data. She used the model to explore the relative roles in bleb formation time of cytoplasmic viscosity and drag between the cortex and the cytosol. Strychalski found that to match the data requires large drag relative to viscosity, suggesting that drag is a dominant force in bleb formation. The model fit the experimental data well, and using the model, she was able to predict the Darcy permeability and the volume fraction of the cortex.

The symbiotic relationship between mathematics and life sciences

Daniela Calvetti -Case Western Reserve University)

In the afternoon plenary, Professor Daniela Calvetti discussed modeling and inverse problems in biology, and in particular going from metabolism to mathematics and back. In human metabolic models, molecular and subcellular phenomena can have whole body effects so multi-scale modeling is often needed. However, the data is usually insufficient to identify the models, making uncertainty quantification important. How does one write down a predictive dynamic model of a cell? The forward problem is to develop a detailed parametric model, and the inverse problem is to infer the model parameters given concentration measurements. In the classical mathematical view of the inverse problem, the central questions are of existence, uniqueness, and stability. In biology, a parametric model is almost invariably insufficient and considering distributions of parameters makes more sense. Thus, inverse problems in biology can be thought of as statistical inference problems. Professor Calvetti's work is in the area of Bayesian statistical inverse problems, where all unknowns are random variables characterized by a probability distribution. She explained the methodology her group has developed in the context of metabolic networks and stoichiometry. Their methods, which involve many steps including numerical algebra, Markov Chain Monte Carlo (MCMC) sampling, and regularization to avoid overfitting to noise, have been made available to the public via the free software Metabolica. Professor Calvetti then went through two example applications: parameter estimation during ischemia in skeletal muscle, and analysis of brain metabolism. For brain metabolism, she considered a three-partite model with glutamatergic neurons (excitatory activity), GABAergic neurons (inhibitory activity), and astrocytes (glial cells). They found that GABAergic

neurons keep up a significant oxidative metabolism level, producing excess of what neurotransmitter cycling requires (in other words, they use a lot more oxygen than we'd expect). Their analysis showed that in their model with three cell types, lactate uptake follows the same partitioning as glucose, but oxidative phosphorylation does not. The explanation of this observation is a topic of ongoing research.

Panel Discussion

The first panel discussion centered on applying for jobs in academia and industry. The topics covered included: putting together application materials (letters, research/teaching statements, cover letters, CV tips), how to decide what department is a good fit, applying to research universities vs. liberal arts colleges, how to tailor applications for academia vs. industry, and interview and negotiation tips. The panelists were Leon Glass (McGill University), Daniela Calvetti (Case Western Reserve University), Elizabeth Marschall (The Ohio State University), Jim Cushing (University of Arizona), and Elizabeth Allman (University of Alaska-Fairbanks).

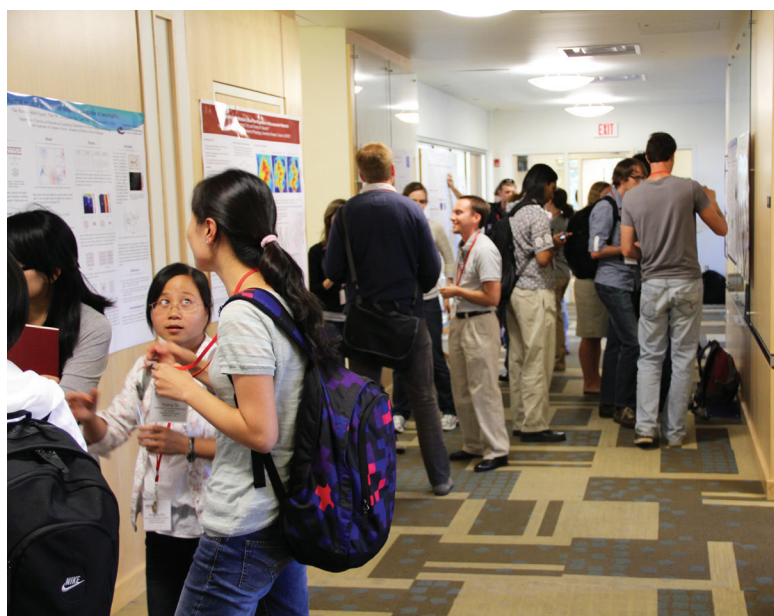
Tuesday

Phylogenetic tree models: An algebraic view

Elizabeth Allman - University of Alaska Fairbanks

Professor Elizabeth Allman began the morning plenary by introducing a range of questions in phylogenetics, some basic concepts in phylogenetic trees, and an overview of the probabilistic framework used when looking at tree models. Her research takes an algebraic approach to looking at phylogenetics, using algebraic invariants as a way of specifying the phylogenetic tree. To that end, she next introduced some of the basic algebraic concepts needed for her talk (e.g. ideals, varieties). To each tree, one associates a phylogenetic variety, and from the associated phylogenetic ideal one can find phylogenetic invariants which must be satisfied for a given tree to match a data set. Although in principle the phylogenetic invariants can be computed (e.g., via Gröbner bases), in practice this is often computationally infeasible. She introduced several theorems and methods that allow one to gain insight from phylogenetic ideals and varieties, such as using flattenings to generate invariants. She next discussed some identifiability issues in phylogenetics. A series of recent papers suggested that a commonly used class of models is uniden-

tifiable—however, they were able to show that these unidentifiable examples are nongeneric. She also discussed questions that arise when looking at gene trees versus species trees. Allman introduced a multi-species coalescent model, where we see some examples of the possible gene tree topologies for a given species tree, and explored some of the recent work in this area. She concluded by noting that statistical models in phylogenetics have a rich algebraic structure, and by using an algebraic geometry viewpoint to examine these models, new insights can be found.



Panel Discussion II

The second panel discussion centered on career development in mathematical biology. Topics covered included the tenure process, career development/opportunities in industry, starting collaborations, developing a research program, applying for grants (tips for grant applications, grant opportunities for young investigators), and work/life balance issues. The panelists were Julien Arino (University of Manitoba), Jeff Saltzman (Astra Zeneca), Feilim Mac Gabhann (John Hopkins University), Leon Glass (McGill University), Elizabeth Allman (University of Alaska-Fairbanks), and Jim Cushing (University of Arizona).



Jim Cushing

Mathematical Modeling of Hepatitis Type C Virus in a Pharmaceutical Context

Jeffrey Saltzman -Astra Zeneca

In the afternoon plenary, Jeff Saltzman gave an overview of how applied mathematics is used within the pharmaceutical industry. Applied mathematics and, more generally, quantitative sciences are seen as important capabilities having the potential to address the current scientific and economic challenges being encountered by this industry. In his presentation Dr. Saltzman gave an insider's view of the pharmaceutical drug development process, the pressure points stemming from economic and scientific pressures and where critical applications of mathematics must be achieved. As a case study, Dr. Saltzman described the mathematics brought to bear modeling the evolution and treatment of Hepatitis type C virus (HCV). A diverse set of techniques were applied including ordinary and stochastic differential equations, asymptotic analysis, nonlinear mixed effects models and partial differential equations. These mathematical tools help draw a picture of the treatment and serious side-effects from attempting to cure HCV with the current standard of care. To wrap up, Dr. Saltzman emphasized that modeling is a team

sport involving collaborations across the pipeline from discovery scientists to clinicians. Although the process is messy and unsystematic, each new model contributes towards the aspiration of an in-silico pipeline.

Novel Patterns and Dopamine Modulation in a Model of Working Memory

Robert A McDougal -Ohio State University

Robert McDougal opened the afternoon short talk session by describing a model of working memory-- the process for the short-term storage and manipulation of information necessary for complex cognitive tasks. During the performance of working memory tasks, the prefrontal cortex (PFC) exhibits sustained persistent activity and is believed to play a key role in the process. Experiments have demonstrated that working memory performance is modulated by dopamine, which is known to be altered in certain pathological conditions, including schizophrenia. A number of models have been proposed for the maintenance of persistent activity in the PFC, often based on either intrinsic cellular bistability or recurrent excitatory connections formed via synaptic adaptation. McDougal presented a new approach consistent with the observation that inhibitory connec-

tions dominate the PFC: a network driven by excitatory-inhibitory interactions where the response to inhibition is modulated by intracellular calcium. Individual neurons fire irregularly, but the model network exhibits emergent properties, such as a clear gamma rhythm. The network is robust to noise and distracters. Only general assumptions about connection probabilities are assumed; the model can represent novel, unlearned stimuli. Dopamine modulates ion channel activity and synaptic conductances. McDougal studied the effects of this modulation on cellular and network behavior, and was able to reproduce the experimentally-observed inverted-U shaped relation between dopamine expression and working memory performance.

A stochastic multi-scale model of fibrinolysis

Brittany Bannish -University of Utah

Brittany Bannish's talk focused on modeling the breakdown blood clots. The degradation of blood clots is a tightly regulated process. If the mesh of fibrin fibers securing the clot degrades too slowly, thrombi can form, leading to heart attack or stroke. If the fibrin degrades too quickly, excessive bleeding may occur. Banish studied fibrinolysis (the degradation of fibrin by the main fibrinolytic enzyme, plasmin) using a multi-scale mathematical model intended to answer the following question: Why do coarse clots composed of thick fibers lyse more quickly than fine clots composed of thin fibers, despite the fact that individual thin fibers lyse more quickly than individual thick fibers? She used stochastic methods to model lytic processes on scales ranging from individual fiber cross-section to whole clot. Banish found that while fiber number does have an effect on lysis rate, it is not simply "fewer fibers equals faster lysis", as many biologists suggest. In fact, the number of tissue-type plasminogen activator molecules (tPA, an enzyme that converts plasminogen to plasmin) relative to the clot surface area exposed to the tPA strongly influences lysis speeds. She also predicted how many plasmin molecules can be produced by a single tPA molecule, how long it takes a given number of plasmin molecules to degrade a single fibrin fiber, and how patterns and speeds of lysis (both on an individual fiber and clot scale) vary under a range of conditions. This last point is of particular interest for development of treatments for occlusive blood clots. Often, a bolus of tPA is injected near the thrombus, in an attempt to initiate therapeutic lysis. Her model predicts other potential

targets for future research on effective therapeutic strategies for degrading blood clots.

Transient Vector Field Effects on Oscillations in a Neuromechanical Model of Limbed Locomotion

Lucy Spardy -University of Pittsburgh

In the final talk of the day, Lucy Spardy analyzed a closed-loop locomotor model in which a central pattern generator drives a single-joint limb and receives afferent feedback. Transitions associated with changes in ground reaction force or motoneuron outputs abruptly altered the vector field in the limb dynamics phase plane. The positions of the locomotor oscillation trajectory relative to these transient vector fields and their critical points explain the model's ability to replicate an experimentally observed locomotor asymmetry. A contraction argument relying on these transitions provides conditions for existence of a periodic orbit in a reduced model.

Wednesday

The spatio-temporal spread of infectious diseases

Julien Arino -University of Manitoba

Professor Julien Arino discussed diseases in metapopulations. He began with some background on disease spread, using a quote by Thucydides to note that even in 400 B.C., people noticed the spatiotemporal spread of disease. Early spatial spread of disease was slow and spread more diffusively, but with modern day rapid travel (cars, air travel), spatial spread can be much faster, and pop up in seemingly unrelated places. The 2002-2003 SARS epidemic provides a recent example, where air travel was key to disease spread. Prof. Arino introduced a movement framework for metapopulation models, using and SEIRS (Susceptible-Exposed-Infectious-Recovered-Susceptible) as a base. He developed the mathematical framework, and overviewed some of the results that can be proven for this class of models. Next, he looked at these issues from a more public health oriented perspective, and introduced us to the biodiaspora project, which examines how information on the global air transportation network can affect disease spread. They took multiple flight data sets detailing the flights scheduled between all major cities of the world, and combined this with data on local conditions, travel data, and health map surveillance to build a global connectivity model, which incorporates seasonality of travel between nodes (airports). From this model, they

were able to unravel a range of insights about air travel patterns, and evaluate the effectiveness of interventions such as canceling flights. In examining the H1N1 flu of 2009, they found that flight cancellation had little effect on disease spread, as it was relatively easy for passengers to re-route their flights through an alternate airport. They were also able to simulate hypothetical scenarios for different diseases and see how an epidemic would be likely to spread.

A New Route to Periodic Oscillations in the Dynamics of Malaria Transmission

Calistus Ngonghala -West Virginia University

Next, Calistus Ngonghala discussed modeling malaria transmission. He began with an overview of both the public health and life cycle of malaria. Their goal is to develop a new model which accounts for the developmental stages of the model, which they can use to propose control methods. The model is a basic SIS model of human disease dynamics, coupled with a multi-stage model of malaria in the mosquito vector. He then presented the analysis of the model. The disease free equilibrium simplifies to being dependent only on the dynamics of the vector, and they found a threshold parameter that ensures stability of the no-mosquito equilibrium when less than 1. This is impractical as mos-

quitoes are important ecologically, however they also found a threshold parameter for the disease free mosquito case. They showed that the endemic steady state solution can be driven to instability via a Hopf bifurcation, and also found a backward bifurcation, meaning that reducing the basic reproductive number below one may not be enough to eradicate disease. These results highlight the importance of considering the mosquito life stages in modeling malaria. He closed by discussing some of the upcoming extensions to the model, such as incorporating multiple human locations and multiple breeding sites for the vector.

A game theory approach to infectious disease management policy through individual and government investments

Jing Li -Penn State University

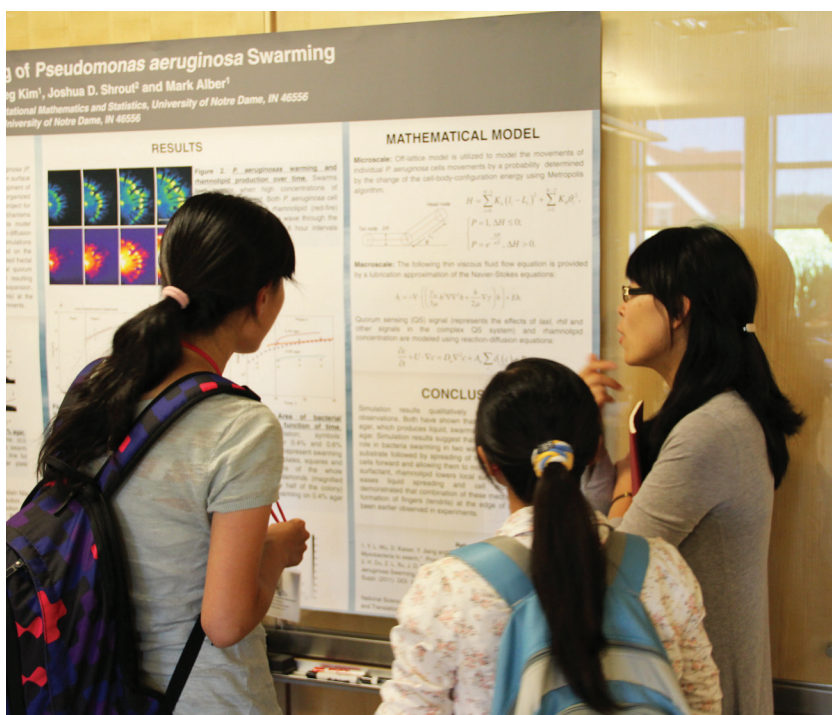
Next, Jing Li discussed some of the interactions between government and individuals in infectious disease management. She began with a quick introduction to the SIR framework of epidemic models she is considering, and an overview of some of the interventions possible by individuals and government (e.g., individuals can wash their hands, governments may institute vaccination campaigns, etc.). She is interested in examining how individual perceptions change depending on government action. The response of individuals to disease

may change depending on government policy, and these interactions can lead to unexpected effects. She formulated a population game to explore how individual investment through behavior and government investment through taxation impact the health commons. Using this framework, she examined how different government policies interact with individual perception, and found conditions for when individual and government actions are independent.

Application of Lie group Analysis to a Mathematical Model which describes HIV-TB

Matadi Maba -University of KwaZulu Natal

Next, Matadi Maba discussed a model of HIV and tuberculosis coinfection. The model divided individuals into ten classes, using a SEIR (susceptible-exposed-infected-recovered) type of framework.



They began by examining the HIV submodel. The initial exploration showed an infinite number of Lie operators, however they were able to reduce the dimension of the system and apply Lie analysis to find an explicit solution to the differential equations. They found an eight dimensional Lie symmetry algebra, which allowed them to linearize their equations and find an explicit solution. Using a similar analysis, they were able to find an explicit solution for the tuberculosis submodel as well. Maba closed by discussing future work in which he hopes to use a similar approach to analyze the full model as well.

Models for Semelparity: Dynamics and Evolution

Jim Cushing -University of Arizona

After lunch, Professor Jim Cushing discussed the question of existence versus persistence in population dynamics. He began with exploring how species allocate resources to growth, survival, and reproduction. He discussed what possible tradeoffs there might be between these factors, and how to time reproduction accordingly. Next, he introduced semelparity, wherein an individual has one time period for reproduction in its lifetime. He introduced the modeling methodology used here, namely semelparous Leslie matrix models, and then described work with an interdisciplinary team wherein they examined whether calibrated models can make accurate, quantitative predictions in population dynamics. Over the course of several years, they built a series of models that accurately describes the dynamics of flour beetles, and in fact makes subtle predictions about the population dynamics that they were able to verify with experiment. Using the model, they were able to use experiments to take flour beetles through bifurcations and show chaotic dynamics, which has since been called the first unequivocal example of chaos in population dynamics. Prof. Cushing developed some of the theoretical framework for matrix models, discussed their connections to experiments, and closed with some of the evolutionary questions that come up for semelparity, such as how semelparity might be driven by evolution.

An eigenvalue optimization problem in mathematical ecology

Alan Lindsay -University of Arizona

In the first short talk of the afternoon, Alan Lindsay considered habitats with fragmented or concentrated resources. Such fragmentation may occur naturally or as a consequence of human activities related to develop-



Elizabeth Allman

ment or conservation. Determining whether fragmentation is a benefit or hindrance to a species' well-being is a natural question to ask in ecology. In a certain mathematical formulation of this problem, one is led to study an indefinite weight eigenvalue problem, the principal eigenvalue of which is a function of the habitat's make-up and indicates the threshold for which the species either persists or becomes extinct. For a particular but general class of fragmentation profiles, this threshold can be calculated implicitly and optimized to reveal a definitive strategy for minimizing the persistence threshold and thereby allowing the species to persist for the largest range of physical parameters.

Asymptotic growth rates underestimate the transient response of a tropical plant population to harvest

Orou Gaoue -NIMBioS, University of Tennessee

Next, Orou Gaoue discussed the ecological effects of harvesting wild plants as a source of food and medicine. Over the past two decades, mathematical models of such harvesting have used stationary population growth rate as the metric to measure effects of harvest. In his talk, Gaoue showed that using asymptotic rather than the transient growth rates might underestimate the ef-



Daniela Calvetti talk - question and answer.

fect of harvest and of other disturbances. The transient growth rate and its variation between population-level harvest intensities (high versus low) were smaller than their asymptotic equivalent. Patterns of elasticity of transient growth rates to perturbation of vital rates were different from those of the asymptotic elasticity. Asymptotic growth rates were more elastic to perturbation of late life stages; however, transient growth rates were more elastic to early life perturbations. These results suggest that the more than fifty published studies on the effects of harvest on wild plant population dynamics using only asymptotic growth rates may have been underestimating such effects in the short-term.

Thursday

Mathematical Modeling of Angiogenesis

Feilim Mac Gabhann - Institute for Computational Medicine, Johns Hopkins University

In the final plenary talk, Professor Felim Mac Gabhann discussed multiscale modeling of angiogenesis (neovascularization). To grow beyond a certain size, tumors secrete growth factors such as VEGF (vascular endothelial growth factor) to promote sprouting of nearby blood

vessels. Therapies targeting angiogenesis can be useful in diseases where the problem is too many vessels (i.e. cancer) or too few vessels (i.e. ischemia) by inhibiting or promoting VEGF signaling. Professor Mac Gabhann and collaborators have developed mathematical models to study the effects of such therapies in both in vitro and in vivo settings. The first model Prof. Mac Gabhann presented was a compartmental ODE model at the tissue, cellular, and molecular levels used to investigate peripheral artery disease. For example, they conducted a 7-day simulation of a person who exercised on 3 days that yielded insights into multi-organ VEGF shuttling mechanisms and extravasation of anti-VEGF. Next Prof. Mac Gabhann described a 3-D multiscale PDE model of skeletal muscle including blood flow, tissue oxygen distribution, and VEGF secretion. These modules were combined with an agent-based model of capillary formulation to simulate blood vessel formation when training at high altitudes. The third part of Prof. Mac Gabhann's talk focused on experimental results of collateral capillary arterialization in mouse skeletal muscle. Using confocal microscopy, Prof. Mac Gabhann compared the architecture of microvascular networks in an ischemia-vulnerable strain of mice (Balb/c) to an ischemia-pro-

tected strain (C57). To illustrate the difference between the capillary networks in different mice strains, Prof. Mac Gabhann used the analogy of roadway systems. In Ireland and Europe, the major city in a country typically has a ring road, and then smaller roads radiating out. If a particular road into Dublin is closed, then you will often be re-routed onto a much smaller road adding a lot of time to the trip. This architecture is analogous to the capillary network in Balb/c mice. By contrast, the United States interstate system is more like a mesh, and if the road you usually travel is closed, there is likely another road of similar size that you can take instead so that less time is added to the trip. This architecture is analogous to the vascular network in C57 mice, offering an explanation for the longer time required for blood flow recovery in Balb/c hindlimb ischemia relative to C57.

Exploring the dynamics of CRISPRs: How much can a bacterium remember about viruses that infected it?

Lauren Childs -Georgia Institute of Technology

Lauren Childs opened up the last short talk session by discussing a novel bacterial defense system against invading viruses, known as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR). Unlike other bacterial defense systems, CRISPRs are virus-specific and heritable, producing a form of adaptive immune memory. Specific bacterial DNA regions, CRISPR loci, incorporate on average 25 copies of unique short (~30 base pair) regions of viral DNA which allow the bacteria to detect, degrade and have immunity against viruses with matching sub-sequences. Ideally, the number of unique viral-copied regions a CRISPR loci contains would grow indefinitely to allow immunity to accumulate to a large number of viruses. However, the number of these viral-copied regions in the CRISPR loci of any bacteria is limited in length and number. Childs used a birth-death master equation model to explore the growth and decay of the length of the CRISPR loci and thus the number of viral-copied regions. Additionally, she used a simple probabilistic model to determine bounds on the length of viral-copied region within the CRISPR locus.

Modularized Smad-regulated TGF β Signaling Pathway

Yongfeng Li -Universities Space Research Association

Next, Yongfeng Li gave a talk on the transforming Growth Factor β (TGF β) signaling pathway, a prominent regulatory signaling pathway controlling various important cellular processes. It can be induced by ion-

izing radiation, and is regulated by Smad in a negative feedback loop. This feedback operates by promoting the nuclear import of the regulatory Smad and subsequent expression of the inhibitory Smad, which forms ubiquitin ligase with Smurf to target active TGF β receptors for degradation. Li proposed a mathematical model to study the Smad-regulated TGF β signaling pathway. By modularization, he was able to analyze each component subsystem and recover the nonlinear dynamics of the entire network system. Furthermore, numerical simulation offered insight into excitability along the TGF β signaling pathway.

A stochastic framework for discrete models in systems biology

David Murrugarra -Virginia Tech

In the final talk, David Murrugarra introduced a new modeling framework for gene regulatory networks that incorporates state dependent delays and is able to capture cell-to-cell variability. This framework was presented in the context of finite dynamical systems, where each gene can take on a finite number of states, and where time is also a discrete variable. The state dependent delays represent the time delays of activation and degradation. One of the new features of this framework is that it allows a finer analysis of discrete models and the possibility to simulate cell populations. The applications presented involved controlling the outcome of lambda phage infection of bacteria, one of the best-known stochastic regulatory networks.

Forward Looking Session

The workshop closed with a forward looking session discussing frontiers in mathematical biology, examples of exciting recent advances in math biology, areas of biology ripe for mathematics to be useful, and how biology can inspire new mathematics. The panelists were Vlastimil Krivan (University of South Bohemia), Anastasios Matzavinos (Iowa State University), David Terman (The Ohio State University), Feilim Mac Gabhann (John Hopkins University), and Elizabeth Allman (University of Alaska-Fairbanks).

Spatio-Temporal Dynamics in Disease Ecology and Epidemiology

October 10-14, 2011

Organizers: Rongsong Liu, Jianhong Wu, Xingfu Zou, and Jean Tsao

Report by: Juan Gutierrez, Paul Hurtado, and Rebecca Tien

Monday

Overview of Spatial Models in Epidemiology

Ben Bolker -McMaster University

Dr. Bolker surveyed methods and issues in spatial ecology. His talk centered about the themes of reducing dimensionality, determining interaction between properties of a model, and finding summary metrics for spatial behavior. He explained several paradigms of spatial modeling, such as metapopulations (or pseudo-spatial models), network models, networks of patches, and reaction-diffusion models. He then presented several general examples and issues such as the linear conjecture for asymptotic wave speed, integro-differential models, lattice models, correlation/moment equations, effects of heterogeneity, challenges of large-scale simulation, and statistical approaches. Finally, Dr. Bolker discussed raccoon rabies in the northeastern US and the UK foot and mouth disease epidemic of 2001.

Differences in the ecology of tick-borne vs. mosquito-borne pathogens, and the implications for modelling, surveillance and management

Howie Ginsberg -University of Rhode Island

Dr. Ginsberg started with considerations about the balance between conservation and public health in regards to environmental management of tick-borne and mosquito-borne zoonoses. He proposed a simple and powerful technique for integrated pest management based on a binomial distribution of the probability of being bitten by at least one infected vector (P) as a function of the proportion of vectors infected with pathogens, i.e. prevalence (p), and the number of vector bites (N): Dr. Ginsberg explained the life cycle of ticks and its effect on Lyme disease, and explained approaches to managing ticks and tick-borne disease as a function of proportional reduction in vectors vs. prevalence (p), showing

that habitat manipulation and manipulation of host populations are the intervention measures that have the most substantial effect. He then explained the differences between transmission patterns of West Nile virus (WNV) vs. Lyme disease. He presented the spatial and temporal factors in the dynamics of WNV transmission, such as presence, density and proximity of competent vectors, competent reservoirs, and humans. Finally, he contrasted the implications for surveillance and management of Lyme disease vs. WNV: (1) To manage of Lyme disease, surveillance has to be done yearly and intervention on spring; to manage , surveillance has to be done in the previous and present year, and intervention the previous year. (2) To manage and of WNVs, surveillance has to be done frequently and intervention has to be based on surveillance.

Temporal dynamics of vector ticks in the southeastern United States: implications for maintenance of the Lyme disease pathogen

Graham Hickling -University of Tennessee, Knoxville

Dr. Hickling presented two case studies: (i) Brushtail possum (introduced from Australia) infecting cows with *Mycobacterium bovis* in New Zealand; the case was made that spatial analysis was indispensable to produce an effective intervention capable of containing the disease; pulse control was shown to have dramatic effect in reduction, but insufficient to produce local extinction of possums, and (ii) Lyme borreliosis vector and agent, particularly the question “Why is the incidence of Lyme borreliosis so low in the southeastern United States even though the vector tick is widespread in that region?”; in this case the spatial analysis needs to take into consideration a careful modeling of temporal dynamics due to the multi-year population dynamics of ticks resulting in nymphs and larvae having a very small temporal overlap in the south and a high overlap in the north. The take-home message is that temporal dynam-

ics should be understood “well enough” before considering space.

Modelling vector-borne disease spread - the example of Lyme disease in Canada

Nicholas Ogden -Public Health Agency of Canada

Dr. Ogden presented considerations about the expansion of Emerging Infectious Diseases (EID) as a result of climate change, from the point of view of public health management. He pointed out that 75% of all EIDs are zoonosis, and raised the question “What tools does public health need if we are to predict and prevent rather than respond to outbreaks?” The case study was the spread of Lyme disease as a function of the spread of its vector, *I. scapularis*. The alert map of Quebec 2004 was presented, along with a discussion on calibrating the spread and routes of disease. The conclusion of this talk is that modeling can assist policy-making, surveillance, risk assessment and response programs.



Joe Tien

Tuesday

Optimal control of spatial and temporal epidemic models

Suzanne Lenhart -University of Tennessee, Knoxville

Dr. Lenhart talked about two different models of rabies in raccoons (a PDE model and a model discrete in time and space) and how these were used to determine optimal strategies to control rabies by distributing vaccine baits. This work is ongoing in collaboration with the USDA. The discrete model is a multi-patch SIR model incorporating vaccine bait dynamics. The analogous PDE version is a spatial SIR model with vaccine control. Using data from Connecticut and an extension of Pontryagin's Maximum Principle that applies to models with discrete time and space, they have developed computational tools to find optimal control strategies using vaccine baits. Some of their results include that the optimal bait distributions depend on both the spatial distribution of disease as well as raccoons, and in many cases the optimal strategy includes “blocking” in the infection by distributing vaccine around the infected areas. The methods used can be extended to other models of this

system and to other forms for the objective functionals used for control.

Disease control strategies influenced by spatial and temporal heterogeneity

Zhilan Feng -Purdue University

Dr. Feng began by showing a simple SIR model of influenza with no demographic dynamics and with a seasonal transmission rate. She described its predictions for the size and timing of the fall outbreak shortly after the start of the 2009 H1N1 epidemic. These predictions were published in late October 2009, and subsequently this simple model did a surprisingly good job at predicting the progression of the fall epidemic. Next, Dr. Feng introduced a version of this model with spatial heterogeneity that was used to study the 2008 outbreak of measles in San Diego, CA where the vaccination opt-out rates are as high as 1 in 10. Using a metapopulation SIR model, she found (among other results) that heterogeneity and non-random mixing can increase epidemic size, and (at least in San Diego) that eliminating non-medical vaccine exceptions would have the same effect as increasing vaccine coverage by 50%. In summary, her



work extended the notions of proportionate mixing rates and preferential mixing rates to better capture observed contact processes between age groups in susceptible host populations. The goal was to see how these heterogeneous mixing processes affect optimal vaccination strategies. Results show that increasing the strength of these non-random/preferential contact rates results in more disease transmission (increased R_0) for a given level of vaccination coverage.

Run for your Life

Odo Diekmann -Utrecht University

Dr. Diekmann introduced participants to ongoing work that revisits the general epidemic model introduced in 1927 by William Ogilvy Kermack and Anderson Gray McKendrick. The aim of the talk was to revive the spatial variant of this nonlinear renewal model, as studied in the late seventies by Diekmann and Horst Thieme. Diekmann expanded the model by incorporating an age-structured population on a spatial domain. The key result is a characterization of the lowest possible speed

of travelling waves, c_0 , and a proof that c_0 is also the asymptotic speed of epidemic propagation.

A Reaction-Diffusion Malaria Model with Incubation Period in the Vector Population

Xiaoqiang Zhao -Memorial University of Newfoundland

Dr. Zhao presented work using a nonlocal, time-delayed reaction-diffusion model to characterize how the spatial heterogeneity and a parasite incubation period in the vector affect the dynamics of malaria epidemiology. He introduced the basic reproductive ratio for this model and showed that it serves as a threshold parameter for malaria spread. He also showed a sufficient condition to guarantee that the disease will eventually stabilize at a positive steady state in the case where all the parameters are spatially independent. Dr. Zhao also presented results with vaccination incorporated into the model. This work was conducted with Dr. Yijun Lou and Dr. Zhit-ing Xu.

Wednesday

Modeling human risk for tick-borne pathogens in the United States

Maria Diuk-Wasser -Yale University

Dr. Diuk-Wasser described the basic biology of Lyme disease, which is caused by *Borrelia burgdorferi* and transmitted to humans by ticks. Similar zoonoses are caused by other tick-borne microparasites including other *Borrelia* sp., *Babesia microti*, and *Anaplasma [Ehrlichia] phagocytophilum*. A key predictor of exposure risk is tick density, larva and nymphs in particular, which is influenced by many factors including the abundance of *Peromyscus* mice. She then showed how climate and landscape data (in conjunction with surveys of tick larva and nymph abundance) could be used to make risk maps for Lyme exposure. Importantly, climate differences can affect the timing of peak larva and nymph abundances. Years in which these peaks have little overlap are associated with increased prevalence of *B. burgdorferi*. Dr. Diuk-Wasser also discussed a second tick-borne parasite of concern, *Babesia microti*, which spreads more slowly than Lyme despite similar incidence in ticks as *B. burgdorferi*. Birds don't appear to be as susceptible to *Babesia*, and may play a role in limiting the spatial spread of this parasite.

Assessing spatially-dependent risks of disease-emergence

Tim Reluga -Pennsylvania State University

Dr. Reluga investigated disease emergence first non-spatially, then spatially. He began with the "stuttering chain" model of zoonotic disease emergence, and some of the potentially important biological processes omitted from this model (e.g. manipulation of the host immune response by the parasite, acquired immunity among hosts, etc.). Dr. Reluga then introduced using Galton-Watson random variables for specifying stochastic models of population dynamics, in particular a (reducible) branching process model of multi-strain disease transmission from a reservoir population to a novel host population. He used this model to explore the role of different routes of transmission (e.g., vector-borne vs. direct) and how emergence probabilities are affected by rates of within- vs. between-species transmission events. Dr. Reluga then introduced a continuous spatial domain to these models to assess the importance of physical barriers and how different spatial locations of disease introductions impact emergence probabilities.

By also adding continuous time to the model, evolution equations for the state of the system were obtained using generating functions for continuous time processes. These yield diffusion equations for the time-evolution of the expected state of the system. Dr. Reluga showed results for similar models (e.g., using an Ornstein-Uhlenbeck model of host movement) and discussed future directions for extending this work to include life history constraints and more specific forms of individual dispersal.

Host-level drivers of infectiousness and susceptibility in birds: implications for emergence and spread of pathogens

Jen Owen -Michigan State University

Dr. Owen described the high variability of viral loads across infected birds, and how this violates a common modeling assumption that individuals are more homogeneous. The case study was avian influenza in mallard populations. It was shown that some individuals exhibit high pathogen loads (termed 'super shedders') whereas others maintain low pathogen loads. Experiments on captive birds demonstrate that those in poor condition shed less virus than birds in normal condition. Moreover, different strains varied in their ability to infect the gut vs. the respiratory tract. In general, a high degree of heterogeneity was observed. Dr. Owen then discussed studies of other pathogens and host species that demonstrate similar effects of stress and physical condition on a host's susceptibility and infectiousness. Dr. Owen's presentation highlights the pervasiveness of high variability across individual infections caused by multiple sources of individual heterogeneity. This underscores the need to develop and employ new modeling approaches to better understand the causes and consequences of this variation.

The dynamics of "contact" via coughing and sneezing

Lydia Bourouiba -MIT

Dr. Bourouiba began with an overview of the global burden of infectious disease related illnesses and deaths, including airborne infectious diseases. The goal of the research presented is to identify key mechanisms important for indoor respiratory disease transmission and to rethink the notion of 'contact' for respiratory diseases. Coughing, sneezing and other "violent respiratory events" produce infectious droplets that can be functionally categorized as either 'large' droplets that travel

according to ballistic trajectories, or 'small' droplets that are more buoyant and can remain in the air for longer periods of time before contacting a new host. Dr. Bourouiba presented a model that treats these droplets as a multiphase droplet cloud in a fluid (air). The model improves upon other models that, for example, are known to underestimate suspension times and the range of infectious droplet clouds. Dr. Bourouiba's talk concluded with discussion of further work that remains to be done, including improved models of inhalation dynamics and understanding pathogen persistence and changes in the infectiousness of airborne droplets.

Thursday

Cholera dynamics past and present

Joe Tien -Ohio State University

Dr. Tien covered different aspects of cholera outbreaks, including the basics of cholera biology and ecology, suitable basic modeling frameworks, challenges regarding parameterization of these models, and extensions of these models to spatial outbreaks such as the ongoing epidemic in Haiti. Some of the results presented include structural identifiability of model parameters given perfect data, loss of practical identifiability in the presence of noise, and recovery of practical identifiability given additional information on pathogen dynamics in the water (for example through measurements of pathogen concentrations). Different aspects of the Haitian cholera outbreak were discussed, including separation of the outbreak into an initial "invasion" phase and subsequent "persistence" phase.

Dynamics of Some Cholera Models

Pauline van den Driessche -University of Victoria

Dr. van den Driessche discussed several different models of cholera dynamics, together with results on mathematical analysis of these models. These models focused on several different aspects of cholera, including: multiple infectious states of both infected people as well as free-living pathogen; nonlinear incidence functions; nonlinear pathogen "shedding"; time scales of infectivity and immunity. Model types included compartmental ODE models as well as integro-differential equation models. Results include proof of global stability in several of the models, and numerical results illustrating how "hyperinfectivity" and loss of immunity can interact to give disease oscillations.

Basic reproduction numbers for reaction-diffusion epidemic models

Wendi Wang -Southwest University

Dr. Wang discussed disease transmission of three different diseases in mice (Lyme, Rabies, West Nile). The purpose of the study was to obtain R_0 for each disease using general reaction diffusion models. He and his fellow collaborators looked at threshold dynamics for disease dynamics. Using this approach, one can find when R_0 is asymptotically stable vs. persistent. The outcome of the study showed that for all three diseases, the more spatial heterogeneity that existed for the disease vector (in this case, deer) the larger R_0 . (Culling deer in the region created spatial heterogeneity.) They also found that reducing diffusion does not affect R_0 for Lyme disease, but increases R_0 for rabies and West Nile Virus.

Spatial Spread of a Marine Infestation: Ciona intestinalis

James Watmough -University of New Brunswick

Mussel farming is an increasing industry in Atlantic Canada. Vase tunicates act as a nuisance species that grows around mussels and increases the cost of harvesting them. Ignoring anthropogenic spread and focusing on spread by currents, Dr. Watmough took two different modeling approaches. The first model discussed was a continuous time model that explicitly tracked both larval and adult densities of tunicates and showed how they spread to different mussel patches. For the second half of the talk, he discussed a patchy-substrate system that was described as a dispersal network using a matrix model approach. In this case, they modeled how tunicate larvae from infested patches spread via currents to patches that contained seed farms for mussels. There were three outcomes generated from this model: Key nodes between infected and seed sites were identified; infestations could be controlled by treatment of these critical connecting sites; and most importantly, natural spread is not inevitable so anthropogenic spread must be taken into account when considering management of mussel farms.

Dynamics of an SIS Reaction-Diffusion Epidemic Model for Disease Transmission

Wenzhang Huang -University of Alabama, Huntsville

First Dr. Huang gave a general overview of a standard SIS model that incorporates spatial dependence (i.e. a reaction-diffusion model with no flux boundary conditions). He then discussed how he has modified this mod-



Pauline van den Driessche

el to look at the case where the boundary conditions are “hostile” (using Dirichlet B.C.s). The last section of the talk covered the existence of traveling waves that serve to connect disease-free and endemic equilibria. For each model, Dr. Huang discussed the possible outcomes for the spread of the disease based on the value of R_0 (the number of secondary infections generated by a single infectious individual in an otherwise completely susceptible population).

Friday

Insecticide resistance and its implications for mosquito and malaria control

Stephen Gourley -University of Surrey

Dr. Gourley presented his research on the rapid development of insecticide resistance in mosquitos and its importance in malaria control. The speed of evolution in mosquitos is related to how quickly the insecticide kills young adults when the insects come in to contact with it, which leads to strong selection on the young. Weaker selection for resistance is possible if insecticides target only senescent mosquitoes. This system was analyzed using stage structured population models. Predictions were made about the delayed onset of resistance in the mosquito population when exposed to an insecticide that acts only on older members of the population. He also discussed briefly the consequences of mosquito

control using larvicides. One consequence of using larvicides is that larvae can evolve resistance. However, this can actually be an advantage from the viewpoint of malarial control. The reason for this is that the evolutionary cost of larvicide resistance may be reduced longevity of adults. Consequently, the likelihood that the parasites live long enough to complete their developmental stages and spread the disease is reduced.

Spatio-Temporal Dynamics in Disease Ecology and Epidemiology

Shigui Ruan -University of Miami, Coral Gables

Dr. Ruan discussed the effect of human movement in heterogeneous patches on the spread of malaria as well as the contribution of mosquito movement to disease dynamics. Some questions that he raised were whether movement rates for both humans and mosquitos could be backed out from data and whether the difference in scale of the movements of humans vs. mosquitos is important in disease spread. Two modeling approaches were discussed: Lagrangian (track individuals) vs. Eulerian (look at net rates). For each model, he investigated how R_0 depended upon travel rates of humans and mosquitos as well as on various parameters (e.g., travel rate of the infected class) within the models. His results show that the movement of humans between patches is sufficient to maintain disease persistence in patches with zero transmission.

Free Boundary Problems in Biology

November 14-18, 2011

Organizers: Avner Friedman, Miguel Herrero, Luis Caffarelli

Report by: Duan Chen, Harsh Jain and Joaquin Rivera-Cruz

Monday

The dynamics of mucin-like gels, or why your stomach does not digest itself

James Keener -University of Utah

Dr. Keener's talk focused on his recent work in developing a general theory for the dynamics of chemically reactive biopolymer mixtures. In particular, he presented an application of this theory to understanding the role of the mucus layer in preventing the stomach from digesting itself, given that the stomach lumen is highly acidic. Using 2-phase fluid flows to model the secretion, flow and degradation of mucin in the gastric pit, Dr. Keener showed how the free boundary corresponding to the mucin layer edge could be determined by an application of the Helmholtz Minimal Energy Dissipation Principle. The inclusion of measurable rheological parameters gave his model a significant advantage of over traditional approaches. An important conclusion from the steady-state analysis of the model was that unlike in previous theories of gel swelling, the standard free energy of the system couldn't be ignored. Further, including the effect of important ions, such as hydrogen and sodium, lead to a variety of phase transition behavior with even single-well potentials. The inclusion of calcium ionization was predicted to result in the massive de-swelling of gels, a conclusion borne out by experiments. Based on these results, Dr. Keener proposed a mechanism for the secretion and maintenance of the mucin layer, and it's function in providing acid protection and transport. He concluded his talk with an important application of his results in the treatment of cystic fibrosis wherein sticky mucus builds up in the internal organs. Based on the role played by hydrogen and calcium in determining the thickness of the mucin layer, hydration with calcium-free saline solution was predicted to be therapeutic for cystic fibrosis patients.

Free boundary problems in biological tissue growth

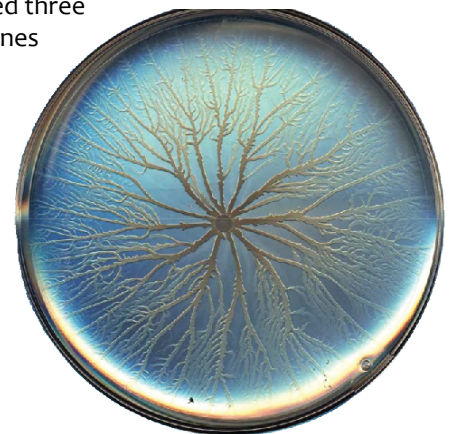
John King -University of Nottingham

In his talk, Dr. King gave a historical overview of his work with his collaborators in free boundary problems biological growth of tissue. In the schematic of his model Dr. King showed us the three phases of tissue growth: (1) an exponential growth initially due to large supply of nutrients, (2) a linear growth phase with the creation of a viable ring where the growth is linear, and (3) a saturation growth where there is a cluster of dead cell at the center of the region. Dr. King discussed the corresponding models, hypothesis and analysis for the tissue growth in each phases. In phase I, the main hypothesis was Darcy's law and the main mathematical issues were the derivation of the phase limits, and the solution for radially symmetric growth. In phase II, the main idea was to take advantage of the short time scales and look at the system at a pseudo-quasi steady-state. Finally the case for phase III was discussed in which now we have a region in the center with negative growth. Dr. King proposed the open question: Are there non-steady state solutions for the system? The talk ended with a list of extensions of this work.

Modeling and computation of biomembranes

Ricardo Nochetto -University of Maryland, College Park

Dr. Nochetto presented three models of biomembranes along with their numerical simulation. The first one is purely geometric since the equilibrium shapes are the minimizers of the Willmore (or bending) energy under area and



Tumor - <http://www.ann.jussieu.fr/~mintang/research.html>

volume constraints. They modeled director fields on flexible surfaces and utilized the shape differential calculus. The second model incorporates the effect of the inside (bulk) viscous incompressible fluid and leads to more physical dynamics. The fluid red blood cells are employed as examples and physical parameters are estimated. The third model describes the interaction of a director field with a membrane, giving rise to an induced spontaneous curvature.

They proposed a parametric finite element method for the discretization of these models and examine crucial numerical issues such as dealing with curvature and length constraints within a variational framework. The finite element stability is studied, a mixed finite element formulation is presented and stability analysis is given. Finally, he showed several simulations describing the dynamics of purely geometric flows, membrane-fluid interaction, and the dramatic effect of defects of the director field on membrane shape.

Regularity for almost minimizers with free boundary

Tatiana Toro -University of Washington

Dr. Toro presented some studies on the regularity of almost minimizers for the types of functionals analyzed by Alt, Caffarelli and Freidman. First she gave an introduction on one phase and two phases problems of minimizers with free boundary. Dr. Toro stated that although almost minimizers do not satisfy an equation, using appropriate comparison functions, they prove several regularity results. For example in the one phase situation, they showed that almost minimizers are Lipschitz. For two-phase problem, it is proved that there exists an absolute minimum and then the solution is locally Lipschitz. Then she compared the minimizers and almost minimizers from aspects of continuity, satisfying an equation or not, and whether they are Lipschitz continuous. For almost minimizers, she first presented that it is proved as continuous and the available tool is comparison functions. Through comparison with harmonic function and iteration, the Poincare's inequality proves the continuity. Furthermore, she displayed further regularity of the almost minimizers and expect it to be Lipschitz continuous. At last, Dr. Toro introduced their ongoing work, which includes the question that are all almost minimizers Lipschitz? Does an almost monotonicity formula hold? For an almost minimizer, what is the



Chuan Xue

non-degeneracy? What is the structure and regularity of the free boundary for almost minimizers?

Tuesday

Modeling blood coagulation: recent trends and new ideas

Antonio Fasano -Università di Firenze

Dr. Fasano's talk focused on resending the biological background and mathematical models for modeling blood coagulation. Biologically, Dr. Fasano described the coagulation process as a 2-step process: (a) primary hemostasis and (b) secondary hemostasis. Dr. Fasano carefully discussed some of the health problems caused by blood coagulation problems (hemophilia) and bleeding disorders. He also discussed the biological concepts and process relevant to the problem, for example: the role of the platelets. He gave a complete survey on the prior studies about blood clotting. Many of the most recent works are described in the form of reaction-diffusion-advection models. Some of these models include a large number of biologically feasible information but with the property that the systems are usually large in the number of PDEs (~50). A simple version consists of an equation (with the corresponding IC, and BC) for

the blood flow, and another equation for the platelets with the free boundary conditions. Dr. Fasano shows that when a slip is added into the model it can have a dominant influence, depending on the geometry of the growing clot. Then he went on to discuss the ingredients and biochemical information to be included in the model. He concluded his presentation by describing all the work that is left to completely analyzed and simulate the boundary value problem.



A hybrid model for tumor growth

Zhan Chen -University of Minnesota

Dr. Chen presented a hybrid model of multicellular tumor spheroid (MCTS) growth wherein a cell-based description is used to model cell growth and division, while a continuum description is used for the quiescent and necrotic zones of the tumor and for the extracellular matrix. Reaction-diffusion equations were used to describe the transport and consumption of nutrients throughout the domain. Dr. Chen argued that his model had an advantage over continuum models of MCTS growth as it addresses cell-cell adhesion, cell growth, cell division and invasive patterning at the cellular level. A hybrid approach ensures that the overall system remains computationally tractable. The model thus formulated had two free boundaries – between the proliferating cell region and the outer gel and the proliferating and quiescent regions – that resembled traveling pulses or square waves. In the model's current version, phenomenological rules implemented numerically to

resolve these free boundaries. It remains an open problem to improve the representation of the boundaries and to derive dynamical properties such as existence, uniqueness and stability. Dr. Chen concluded his talk by showing that the model could predict a number of cellular behaviors that have been observed experimentally. As an example, he presented an application of his work to modeling ductal carcinoma in situ.

Analysis of the Cahn-Hilliard Equation with relaxation boundary condition modeling contact angle

Xinfu Chen -University of Pittsburgh

Dr. Chen's talk discussed the Cahn-Hilliard equation with relaxation boundary condition modeling the evolution of interface in contact with solid boundary. The problem considered is a two fluid flow with the moving boundary given as the intersection of the two fluids. Prof. Chen developed the dynamic of the contact point and the contact angle. He then separated the problem into slow and fast subsystems. For the slow dynamics the resulting reduced problem was on the form of a Cahn-Hilliard equation. Dr. Chen showed that the problem has classical solutions for $N < 3$. The fast dynamics, that is when ϵ tends to zero, was analyzed by taking an asymptotic expansion. Finally, Prof. Chen compared his analytical results with numerical simulations.

PDE tumor models

Bei Hu -University of Notre Dame

Dr. Hu started his talk by presenting a comprehensive survey about prior works in tumor models. Dr. Hu then proceeded to set the general problem in the form of a reaction-diffusion equation for the nutrients and the equation for the porous medium in the tumor region on a variable domain. Dr. Hu showed that for a special case the system is known to have radially symmetric solution. Then using the Crandall-Rabinowitz Dr. Hu analyzed the bifurcation branches and its stabilities by methods of complex analysis. To consider the full-nonlinear problem, the sketch of the work proposed by Dr. Hu was to apply the Hanzawa transformation, and then to linearize the resulting model about the radially symmetric solution. In the numerical simulations, the issue consisted in that the mesh was part of the unknown.



Panel discussion with Avner Friedman, Antonio Fasano, and Jim Keener

Wednesday

Some modeling problems in bone repair

Miguel Herrero - Universidad Complutense Madrid

Under suitable circumstances, bone tissue is able to self-repair small fractures and to integrate external implants. The main aim of Dr. Herrero's talk was to provide the audience with a comprehensive biological background in the complex process of bone repair. In doing so, he pointed out a number of modeling problems that arise from the various steps involved in this process. In particular, the mechanism of osseointegration that refers to bone regeneration around implants is regarded as a major condition for the long-term clinical success of bone implants. This involves the formation of ossification fronts that fill up gaps between the bone and the implants, and therefore suggest free/moving boundary-type problems with travelling wave solutions. In the latter half of his talk, Dr. Herrero briefly presented

a 2-D mathematical model of osseointegration in dental implants, based on a set of reaction-diffusion equations that admitted as variables platelets, osteoblasts, osteogenic cells, growth factors and volume-fractions of the various types of bone tissue formed during implant-integration. Analysis of the steady-states of his model revealed a bifurcation parameter relating to cell stimulation that leads to traveling waves representing propagation fronts of osteogenic cells. Dr. Herrero argued that such modeling could be used to investigate the effectiveness of recently proposed clinical therapies aimed at improving bone implant healing. In his concluding remarks, he pointed out a number of open questions that can be addressed by his models, such as quantifying the role of mechanical stimulation or the impact of microtopography in bone repair.

Free boundary problems in modeling chronic wound healing **Chuan Xue -The Ohio State University**

In her talk, Dr. Xue presented a 3-D model of chronic wound healing based on partial differential equations that was validated by comparison with experimental data. Wound healing is an extremely complex process, involving homeostasis, inflammation, and proliferation of cellular species, vascular formation and remodeling, all of which are tightly regulated by a number of proteins and oxygen. Additionally, the mechanical properties of the extra cellular matrix (ECM) play a crucial role in determining the outcome of wound healing. Dr. Xue argued that her model of this process represented a significant improvement over existing models as it treated the wound boundary as a moving boundary, and accounted for the mechanics of growing tissue matrix by modeling the ECM as a quasi-stationary upper-connected Maxwell fluid with growth. She then presented a few analytical results of her model including the local existence and uniqueness of solutions in the case when the free boundary and fixed boundaries of the wound are orthogonal. However, proving this for a general geometry or in a global sense remains an open problem as does deriving properties of the free boundary.



Bei Hu

In the latter half of her talk, Dr. Xue discussed a model simplification wherein the domain geometry was taken to be 2D with radial symmetry. In this case, assuming homogenized boundary conditions at the wound edge

revealed a critical parameter whose value determined whether or not a wound is predicted to be chronic. For this case, Dr. Xue proved global existence and uniqueness of solutions and derived properties of the free boundary, such as proving that highly ischemic wounds cannot heal. Based on numerical simulations, she proposed the following conjecture, that the degree of ischemia was a bifurcation parameter for the closure of the wound in finite time. In conclusion, Dr. Xue mentioned some ongoing extensions of her work, including a biomedical application of her model where its predictions are used to optimize oxygen dosing in the treatment of chronic wounds, as well incorporating more biological details to improve confidence in her model's quantitative predictions.

Fluctuations in a moving boundary description of diffusive interface growth

Rodolfo Cuerno -Universidad Carlos III de Madrid

Dr. Cuerno first demonstrated the facts that stochastic generalizations of moving boundary problems appear quite naturally in the continuum description of e.g. solidification problems. Then he claimed and presented perhaps the simplest example, a so-called one-sided solidification problem in which a condensed (solid) non-diffusing phase grows at the expense of a diluted diffusing phase (vapor or liquid). In this context, noise terms can be introduced to account for fluctuations in the interface kinetics leading to irreversible growth, and in the diffusive currents in the diluted phase. Thus, an effective closed evolution equation for the interface profile can be derived in a systematic way, carrying both deterministic and stochastic contributions, with parameters that can be related to those of the full moving boundary problem. This effective equation provides an interesting instance in which one can study the interplay between noise and non-local effects induced by diffusive interactions. Going beyond the approximations made in this process requires, e.g., formulation of a (stochastic) phase-field description that is equivalent to the original moving boundary problem. In turn, phase-field simulations allow exploring the rich morphological diagram that ensues. He discussed several applications in the context both of non-living and biological systems subject to diffusion-limited growth, such as surfaces of thin films produced by Chemical Vapor Deposition or by Electrochemical deposition, or bacterial colonies. The



Tatiana Toro

work described was done in collaboration with Mario Castro and Matteo Nicoli.

Parabolic signorini problem

Arshak Petrosyan -Purdue University

Dr. Petrosyan's talk focuses on the regularity of solutions to parabolic signorini problems. First he introduced semipermeable membranes and osmosis, and then gave a mathematical formulation of unilateral problem. This formulation contained osmotic pressure and pressure of the chemical solution, which satisfies a diffusion equation. When one of the parameters goes to infinity, the problem is known as having Signorini boundary conditions, and one phase becomes thin obstacle. Then he presented the variational inequality, from which the existence and uniqueness of solution is proved with reasonable initial condition. Dr. Petrosyan's interests of the problem are the structure, geometric properties and regularity of the solution. After reviewing some known results for some specific cases, he introduced their recent work on optimal regularity of solutions for more general Signorini problems. First, the theorems of optimal regularity of solution to elliptic and parabolic cases are presented. The analysis included normalization, averaged and truncated formula, as well as study of rescaling and blowups. Then the parabolically homogeneous global solutions are studied. Last, he gave a classification of free boundary points.

Thursday

Cell migration as a free boundary problem

Alex Mogilner -University of California, Davis

Dr. Mogilner presented his models of the simplest motile cell – the fish keratocyte. These cells migrate on surfaces by protruding their front through growth of actin networks, retracting the rear by myosin-driven contraction and adhering to the substrate, and maintain a roughly constant shape and velocity. Dr. Mogilner pointed out that any computational framework incorporating the processes involved in cell locomotion would have to treat the cell as an object with a free boundary leading to a very nontrivial mathematical problem. He proposed a mechanical model of the contractile viscous actin gel within the keratocytes that integrates various forces such as the actin-driven protrusion of the cell membrane, membrane tension, cell-substrate adhesion, and myosin-mediated contraction of the actin network, and gives rise to large-scale emergent properties such as cell shape and movement. An extension of this model was able to produce the half-moon steady shapes and movements that are characteristic of keratocytes, based on different minimal mechanisms for cell locomotion such as myosin contraction-driven motility or G-actin transport-limited motility model. The resulting motile cell shapes were shown to be globally stable, underscoring the practical utility of this model. Dr. Mogilner concluded with a model currently under development that could explain the mechanics of cell turning. He proposed that a model with non-constant cell adhesion leads to asymmetries in the myosin flow within the cell resulting in cell turning. This also leads to an interesting open problem – is the motile cell bi-stable? That is, can the same model produce turning motion as well as motion along straight lines?

Propagation of fronts in non-homogeneous media and applications in medicine and biology

Henri Berestycki -University of Chicago

Prof. Berestycki's talk focused on traveling fronts and propagation speed for certain reaction-diffusion equation with applications to medicine. In particular, Prof. Berestycki's talk considered equations in non-homogeneous media. Mathematically, some of the questions he is interested in are these types of problems: (i) is transition waves, (ii) the shape of the front and its propagation speed, and (iii) non-local interactions. The

first problem considered by Dr. Berestycki was the SCD (spreading cortical depression), which is a temporal depolarization related to anomalies on ionic flow (K^+ , Ca^{++} ,...). To model these phenomena Dr. Berestycki proposed consisted in a nonlocal reaction-diffusion in order to study the traveling front solutions and the propagation speed. A second application was the cord tumor growth; these are tumors that grow along a blood vessel. The model consisted of a pair of reaction-diffusion equations, for the cancer cells and the concentration of nutrients. The cancer cells growth logistically with a carrying capacity as a function of the nutrients, and the nutrients decrease proportional. By considering a simple case, the system can be reduced to a single equation, to which Prof. Berestycki showed the existence of a traveling front and a minimum speed. The last application was about climate change where the nonlinear term in the equation drives the existence of the In his presentation Dr Zheng was able to give a short description about the biological process of capillary growth. He then presented his model, but many questions arise in the audience about the well-posedness and existence of solutions. The rest of the talk was dedicated to answer all the questions and comments from the audience, giving little time to Dr. Zheng to finish his talk.

Friday

Free boundary problems in the early development of breast cancer

Yangjin Kim - University of Michigan, Dearborn

Dr. Kim presented biochemically-motivated multi-scale hybrid models of the early development of breast cancer (ductal carcinoma in situ), which focused on the interactions between the stromal cells surrounding the ducts in breast tissue, and tumor cells within the ducts. His models incorporated the different mechanisms by which the local biochemical and mechanical microenvironment affects the progression of cancerous cells. Dr. Kim first presented a validation of his approach by comparing his model predictions with in vitro experimental data. He then generalized this simple model by considering an in vivo situation where mechanical forces from the ductal microenvironment are important. This leads to a free boundary problem where the front of tumor cells growing into the ductal lumen and the outer boundary of the duct represent the free boundaries. In Dr. Kim's formulation, these boundaries were resolved by treating the cells as individual agents, rather than with partial differential equations, as is done classically and modeling the stromal tissue as a visco-elastic





ary method. He briefly introduced the semi-implicit scheme of discretized Stokes equation and fast adaptive composite grid method as preconditioner. Dr. Lee presented cellular movement with concentration dependent contraction and voltage sensitive calcium ion channel gating. He also introduced an immersed boundary method for two-phase fluid and gels, which includes viscoelastic relation and Maxwell fluid model. Last, Dr. Lee showed some examples on collective cellular migration, which has applications in morphogenesis, wound-healing and cancer metastasis.

The structure of the quiescent core in rigidly rotating spirals in a class of excitable systems

Marco Fontelos -Instituto de Ciencias

Matemáticas

material. In particular, his model was able to predict how intracellular signaling pathways mediated by the tumor microenvironment affect the free boundary of a growing tumor in the duct and development of breast cancer, suggesting a potential for application in cancer therapy development.

A viscoelastic model of capillary growth: derivation, analysis, and simulation

Xiaoming Zheng -Central Michigan University

In his presentation Dr. Zheng was able to give a short description on the biological process of capillary growth. He then presented his model, but many questions arise in the audience about the well-posed and existence of solutions. The rest of the talk was dedicated to answering all the questions and comments from the audience, giving little time to Dr. Zheng to finish his talk.

A few examples of moving boundary problems

Pilhwa Lee -University of Connecticut Health Center

Dr. Lee's talk covers several examples of moving boundary problems. The first one is in the single cell level, including fluid-structure interaction and fluid-solute-structure interaction in excitation-contraction coupling in cardiac myocyte and dendritic spine motility and remodeling. Governing equations of Incompressible Stokes flow, advection-electrodifusion and electrostatic potential are coupled in the immersed bound-

Dr. Fontelos first gave an introduction on excitable systems with some examples, and then presented wave propagation in Fitzhugh-Nagumo equation. After showing generation of spiral waves, they propose a model for the core of the spirals. The talk is ended with summary of results and introduction of open problems. The Fitzhugh-Nagumo equation is simplified from the Hodgkin-Huxley model, and then he presented that the system exhibits traveling wave solutions and rotating in the shape of spirals when diffusion term is added to the excitable system. In this talk, they consider the type of Fitzhugh-Nagumo systems that are obtained when considering a simplified version of the Hodgkin-Huxley model for the conduction of electric signals in neurons. The goal is to rigorously prove the existence of spiral waves. The model is classified as quiescent region, stall core, and excited region. An approximation is given which is valid in the areas where potential remains at an excited or quiescent state. The potential jumps from one state to the other at layers of thickness and they take place at a faster time scale. Hence, the equation is rescaled and analyzed in terms of the gradient flow associated with energy functional. The travelling wave solution is found by inspecting similarity solutions of linear function. At last, he summarized that there is a unique solution of the system of ODEs from the spiral fronts and there are solutions connecting the stall region with the outer regions.

Recent Advances in Statistical Inference for Mathematical Biology

February 20-24, 2012

Organizers: Simon Preston, Mark Girolami, Giles Hooker, and Theodore Kypraios

Report by: Arjun Beri, Shu Dai, and Paul Hurtado

Monday

Inference in Mixed-Effects (and other) Models Through Profiling the Objective

Douglas Bates -University of Wisconsin, Madison

Dr. Bates discussed how, in applications, one often needs to know the distribution of a parameter or parameter estimator. This is rarely possible to do analytically, but it can be done computationally. He then introduced a tool for systematically evaluating 1-D profiles of likelihood surfaces (and other objective quantities used in parameter estimation) using mixed effects modeling software developed for the widely used statistical computing software R. Dr. Bates then used some example data (available in the lme4 package in R) to illustrate the visualization and interpretation of these profiles. These profiles are often very skewed, and while that skewness can sometimes be dealt with using log transformations these profiles are typically not well described using summary statistics that assume normality. Dr. Bates also introduced a “sign square-root” transformation useful for visualizing these profiles and using them for certain computations. He concluded with additional examples illustrating how profiling is a useful tool for exploring various aspects of objective surfaces such as likelihood surfaces near maximum likelihood estimates and for discovering non-identifiable (or weakly estimable) parameter pairs.

Inference for partially observed stochastic dynamic systems

Ed Ionides -University of Michigan

Dr. Ionides discussed some of the challenges of using nonlinear mechanistic models for inference and time series analysis, which include properly combining measurement and process noise, incorporating covariates in mechanistically sound ways, dealing with the continuous nature of the underlying biological processes,

dealing with unobserved variables, and spatio-temporal dynamics. He described how Partially Observed Markov Process (POMP) models are frequently proposed as a suitable framework for drawing inferences from time series data using arbitrarily nonlinear, partially observed, vector valued models. This framework enables inference for unobserved states, but numerical methods for inferring unknown parameters or unknown model structure are more problematic. Dr. Ionides then introduced the idea of “plug and play” algorithms; which are algorithms that only require model output (i.e. the ability to sample from the Markov Process) and not an evaluation of the conditional distribution of that model output. Algorithms with the property of being simulation based (as opposed to distribution based) are very useful for scientific applications, although they can sacrifice statistical and numerical efficiency. Dr. Ionides then described using iterated filtering methods for this kind of inference. Two example applications were discussed: coupling a model of malaria transmission with case reports and rainfall data, and modeling measles with overdispersed process noise.

Estimation of ordinary differential equations with orthogonal conditions

Nicolas Brunel -Universite d'Evry & ENSIIE

Dr. Brunel considered parameter inference for ordinary differential equations (ODE) models in the context of nonlinear regression. This approach often leads to poorly posed inverse problems and to challenging optimization problems that result from objectives with multiple minima. He then discussed Gradient Matching, a two-step approach used to surmount these challenges by first fitting the time series data to smooth curves using non-parametric methods, then fitting the ODE model to the derivatives of those smooth curves. For the remainder of the talk, Dr. Brunel introduced the mathematical foundations for a generalization of this approach that

Recent Advances in Statistical Inference for Mathematical Biology

are based upon a weak formulation of the ODE model. Working within the framework of Sobolev spaces, the ODE model is assumed to be L2-Caratheodory and L2-Lipschitz. By considering the variational formulation of such a model, the derived estimators can be viewed as generalized method of moments estimators with statistically and computationally nice properties. Dr. Brunel concluded the talk with some example applications that compare the statistical and practical performance of this approach to the two other approaches mentioned above.

series, the speaker illustrated making inferences about the complicated joint time-varying properties of such observations.

Verification of a biophysical surface protein patterning model: MCMC analysis of dual fluorescence data

Nigel Burroughs -Warwick Systems Biology Centre, Warwick, UK

Dr. Burroughs introduced how to use model fitting to demonstrate the models for segregation and patterning of proteins, and how it is conducive to the separation mechanism. In a lot of biological systems a complex spatio-temporal orchestration of protein relocation is observed, which is called the immunological synapse, occurring predominantly between cells of the immune system. Such structures can be realized in model experimental systems. Existing models explained the observed patterns within certain parameter regimes, whereas how the system is in the parameter regime conducive to separation is unknown. The speaker's group used Bayesian inference to fit a model of fluorescence intensity to single cell data to obtain parameter values. They also determined the degree to which the patterns are consistent with the size dependent thermodynamic model of segregation.



Temporal inhomogeneity and dependence of brain networks **Sofia Olhede -University College London**

Dr. Olhede started with electrical activity of the brain, measured as voltage fluctuations using Electroencephalography (EEG). These measurements are normally made at several locations on the scalp, and the network of activity is inferred from analyzing multiple time series which are neither linear nor stationary. Nonstationary time series are ubiquitous in practical applications. One standard assumption, when deviating from temporal homogeneity, is that in a short time interval there is local stationarity. This simplifying assumption is avoided in recent approaches to these analyses. Using the theory and methods for nonstationary multivariate time

Tuesday

Modeling and inference for gene expression time series data (an overview)

Barbel Finkenstadt -University of Warwick, UK

Dr. Finkenstadt presented an overview of parameter inference from experimental time series measurement, based on stochastic population dynamic models. A 2-D continuous-time Bayesian hierarchical diffusion model was illustrated for the stochastic modeling of transcriptional and translational processes. The inference is complicated since only the protein and rarely other molecular species are observed. For an application on the macroscopic scale, a mechanistic 'switch' model was



Nicolas Brunel

introduced by a switch between periods of transcriptional activity and inactivity. This model has proved to be rich enough to capture a wide variety of expression behaviors including periodic genes.

Inferring the gap between mechanism and phenotype in dynamical models of gene regulation

Dov Stekel -University of Nottingham, UK

Dr. Stekel introduced the method of combining dynamical models with statistical inference as a means to integrate phenotypic data with mechanistic hypotheses. The mechanistic parameters are often difficult or impossible to measure in dynamical models in molecular biology. With the new method, people are able to identify key parameters that determine system behavior and parameters with insufficient evidence to estimate, and thus make informed predictions for further experimental work. Furthermore, inferred parameters can be used

to build stochastic and multi-scale models to investigate behavior at the level of a single-cell. These ideas can be applied to two systems in microbiology: global gene regulation in the antibiotic-resistance bearing RK2 plasmids, and zinc uptake and efflux regulation in *Escherichia coli*.

Statistical Methods for High-Dimensional ODE Models for Dynamic Gene Regulatory Networks

Hulin Wu -University of Rochester

Dr. Wu talked about how to construct a dynamic network for a high-dimensional system, which helps to understand the biological process in a systematic way. The construction is based on coupling a set of ordinary differential equations (ODE) with dimensional reduction by clustering and mixed-effects modeling techniques. The ODE models allow quantification of both positive and negative gene regulation as well as feedback effects, which results in a directed graph network. A five-step procedure, Clustering, Smoothing, regulation Identification, parameter Estimates refining, and Function enrichment analysis (CSIEF) is developed to identify the ODE-based dynamic gene regulatory network. By this method, people are able to annotate the identified modules through function enrichment analyses and constructing more general and complicated dynamic networks becomes possible.

Sloppy Models, Information Geometry, and Data Fitting

Mark Transtrum -University of Texas, M. D. Anderson Cancer Center

Dr. Mark Transtrum presented a technique based on notions of differential geometry to efficiently estimate parameter values of a model from observational datasets. In particular, he introduced the problem of parameter estimation by nonlinear least squares minimization alluding to its geometric interpretation. Finding the best fit of a nonlinear problem is a difficult task, for example, a nonlinear least squares problem may have multiple local minima. In such situations a search algorithm designed to find a global minima, such as genetic algorithm or simulated annealing, is more natural. However, in this work, Dr. Transtrum focuses on the challenge in estimation due to model sloppiness, i.e. sensitivity of the model to parameters. More precisely, the model responds very strongly to a few combinations of parameters known as stiff parameter combinations, and weakly to other combinations known as sloppy parameter combinations. He goes on to illustrate the difficul-

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ties encountered in optimization, namely, occurrence of plateaus and long narrow canyons on the cost contour plots in parameter space. By considering geometric interpretation of least squares model, described by the model manifold in the data space, minimization problem for parameter estimation, thus, translates to finding a point on the model manifold that is closest to the data. The metric tensor is given by the Fisher Information matrix. Model manifolds have various characteristics, such as existence of boundaries, hierarchies of widths, hyper-ribbon, low extrinsic curvature, and parameter-effects curvature. This structure suggests various improvements to the standard optimization algorithms, in particular re-parameterizing of the model with extended geodesic coordinates. He shows that adding a "geodesic acceleration" correction to the standard Levenberg-Marquardt algorithm increases success rate and convergence speed on many fitting problems.

Riemannian Manifolds and Statistical Models: The use of Differential Geometry in Probabilistic Modeling **Ben Calderhead - University College London)**

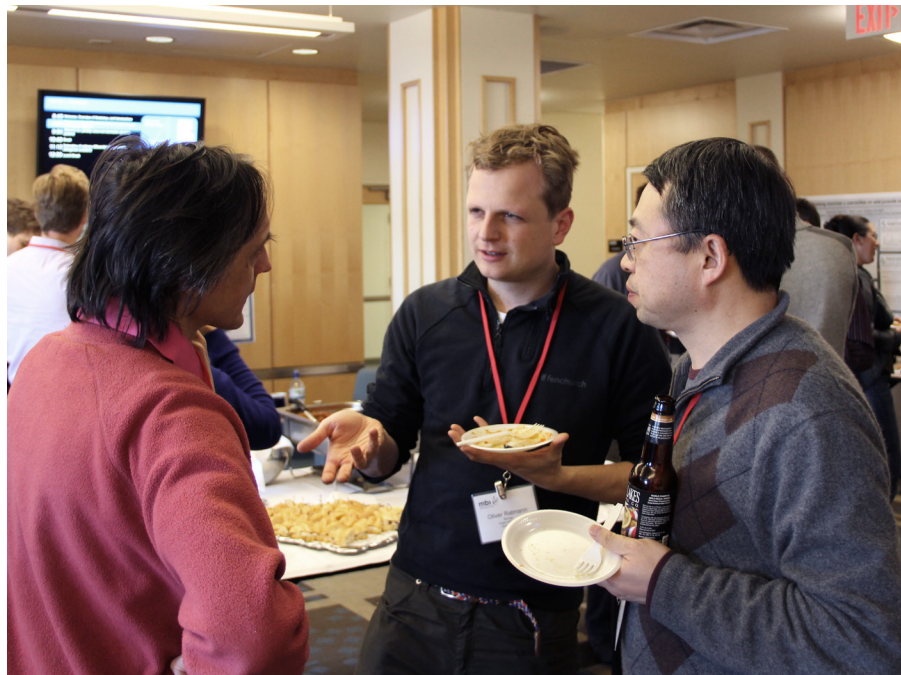
Dr. Ben Calderhead introduced mathematical modeling of biological systems as being entrenched with challenges and complexity, such as sparse uncertain data with unobserved species, potentiality of multiple models for the data, and sensitivity of a model to parameters, for instance ODE models of biochemical networks. Probabilistic approach based on Bayesian technique quantifies uncertainty in both the model parameters, model predictions, and in the model hypothesis themselves. Bayesian approach to statistical inference and model ranking involves, among other challenges, evaluating high-dimensional integrals over the parameter space. Hence, the stochastic integration methods based on Monte-Carlo techniques are utilized. He mentioned that the main issues when designing MCMC algorithms are global convergence, local mixing, and the computational cost. In addition to high-dimensionality,

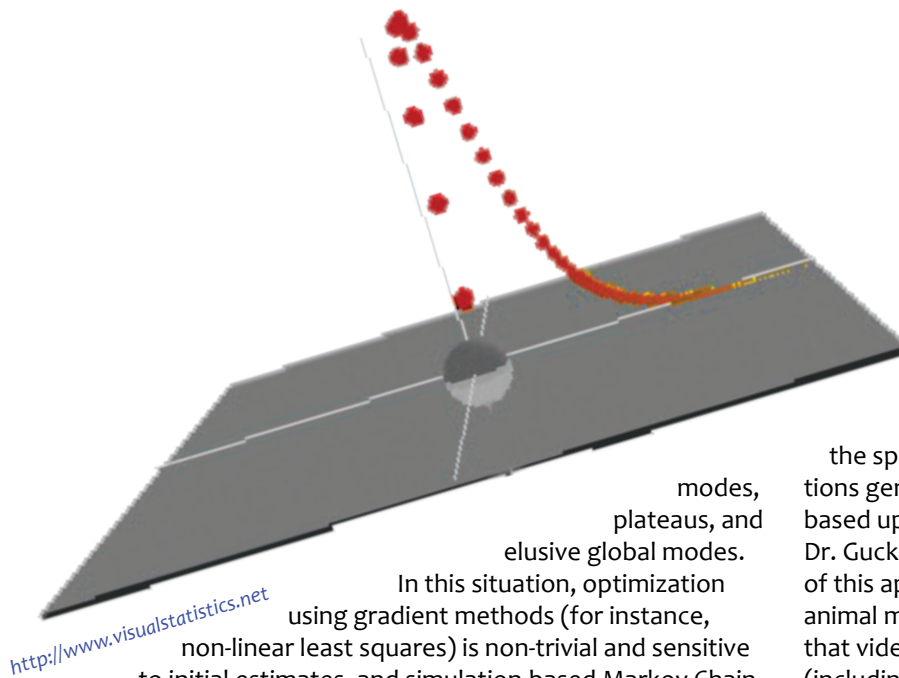
there are difficulties with the strong nonlinear correlation structures and non-identifiability of parameters. In light of these challenges, Dr. Calderhead argued that the recently introduced differential geometric MCMC methodology alleviates many of these issues by making use of the local information. Exploiting the natural representation of the model parameter space as a Riemannian manifold (induced using the expected Fisher information as a metric tensor) allows the MCMC algorithms to be based on the curvature of the manifold that is directly defined by the parameter sensitivities of the underlying model. He then presented application of the proposed method to ODE models describing the circadian clock components in plant *Arabidopsis thaliana*.

Incremental Mixture Important Sampling with Distributionally Relaxed Optimization and Application to Differential Equation Models

David Campbell - Simon Fraser University

Bayesian sampling for parametric estimation of the ODE models is a critical problem in statistical inference of biological systems. Dr. Campbell introduced an 'importance sampling algorithm' to build a posterior approximation based on a weighted mixture of Gaussians. This method, he argues, is useful when posterior densities for differential equations are fraught with ridges, ripples, local





modes, plateaus, and elusive global modes.

In this situation, optimization using gradient methods (for instance, non-linear least squares) is non-trivial and sensitive to initial estimates, and simulation-based Markov Chain Monte Carlo method (in particular, Metropolis Hastings) is likely to get stuck. Then the typical methods are those that deal with optimization by relaxing the model or the likelihood, or are based on the principle of parallel tempering. In particular, Dr. Campbell undertakes a new sequential Monte Carlo "Shotgun" approach, which involves drawing a large sample from a prior, and estimating the likelihood weights to produce a local Gaussian approximation to the posterior. Subsequently, a weighted combination of these Gaussians is used to obtain an approximate sampled from the posterior. Shotgun optimization uses the strength of a lot of methods to explore the posterior from a wide set of starting points. Moreover, most optimizers use single-core computing but shotgun optimization can be performed in parallel. Also, the variation of tempering smoothes out the posterior enabling faster convergence towards dominant mode, and represents an important tool for population-based MCMC simulation.

Wednesday

Dynamical Models of Periodic Processes

John Guckenheimer - Cornell University

This talk introduces ongoing work with collaborator Shai Revzen that aims to extend concepts from Floquet Theory to create a flexible dynamic model framework for building data driven models of dynamic (periodic) biological systems. Dr. Guckenheimer began by pointing out that periodic processes are ubiquitous in biological

systems. Currently, fitting dynamic models to such data often involves measuring perturbations off of asymptotically stable periodic orbits. Floquet Theory models describe the dynamics of the system relaxing from those perturbations back to the periodic orbit, and the goal of this work is to develop a method for building empirical Floquet structure directly from the data.

More specifically, he would like to estimate the spectrum of Lyapunov exponents for such oscillations generically, and to develop reduced order models based upon the weakly stable modes of these systems. Dr. Guckenheimer presented two example applications of this approach. The first was high-speed video of animal movement experiments and derived data from that video. Specifically, the video showed flies in flight (including detailed wing and leg movements) and cockroaches running on treadmills (again, including detailed video of the leg movements) where the limbs involved in locomotion look like noisy oscillators. An analysis of these data showed that they were able to resolve the slow mode of these oscillations using empirically derived return maps.

Errors in variables models: Diagnosing parameter estimability and MCMC convergence using empirical characteristic functions

Subhash Lele - University of Alberta

Dr. Lele began by giving a brief overview of Data Cloning and the related problems of determining whether or not certain factors in a model are non-identifiable and/or non-estimable, i.e. whether or not there is a unique "best" parameter estimate for a given model and data. Non-estimability (and non-identifiability) is particularly problematic when covariates in the model contain substantial measurement errors (i.e. for errors in variables models), and the presence of non-estimable parameters in a model can cause convergence issues with MCMC- and optimization-based computational methods. Data cloning can help identify the presence of estimability problems and this can be seen from certain theoretical relationships between established methods of checking for non-identifiability. For example, the limiting distribution obtained via the Data Cloning procedure is proportional to the inverse of the Fisher Information matrix, which is singular if any parameters are non-identifiable. Dr. Lele discussed different diagnostics used to test for

non-estimability, including sensitivity to the choice of prior, and the use of empirical characteristic functions. To illustrate these diagnostics, he discussed a number of examples. One example was to determine the estimability of parameters for the Ricker model, used by Gauss in his famed Paramecium experiments, which are all estimable even in the presence of (Poisson) sampling noise. Second, he discussed the Theta-Ricker model used by Hassell in a paper with approximately 400 citations. This model was NOT estimable, despite the "Theta Ricker" being similar to the estimable Beverton-Holt version of the model. Dr. Lele concluded by underscoring the utility of checking parameter estimability since it impacts both computational efficiency and since it may impact the conclusions drawn from parameter estimation results.



Modeling and inference framework for studying noise and cell-to-cell variability in synthetic biology

Tina Toni -Massachusetts Institute of Technology

Dr. Toni talked about recent progress on developing modeling and inference techniques to guide design principles in synthetic biology by incorporating noise and cell-to-cell variability. She first presented a schematic of the broader scientific framework illustrating the interplay between modeling and experiments in synthetic biology. She also introduced an example system referred to throughout the talk: the goal of engineering effective cancer-killing cells. Dr. Toni explained that most models only include intrinsic noise and neglect extrinsic noise and heterogeneity among cells: two of the primary causes of variability observed in experimental systems. Dr. Toni then introduced a modeling framework that includes both types of noise, and the use of the Unscented Kalman Filter for doing estimation and inference using this framework. This technique, a refinement of the Extended Kalman Filter, improves the accuracy of how the distributions of model states are propagated through time via non-linear transformations. She then described in greater detail the application of these

techniques to modeling a synthetic circuit that acts as a sensor for micro-RNAs to target cancer cells known to have distinct micro-RNA profiles.

Likelihood-based observability analysis and confidence intervals for model predictions

Clemens Kreutz -Freiburger Center for Biological Systems Analysis

Dr. Kreutz began by describing the challenge of obtaining confidence regions for parameter estimates and for model predictions using nonlinear ODE models. This ubiquitous problem was discussed here in the context of using ODE models of signal transduction networks to resolve certain network structures or to calibrating predictive models. He then introduced profile likelihood as a good "first choice" tool to create such confidence regions. Specifically, he discussed on prediction confidence intervals (PCI) and validation confidence intervals (VCI) which are used to interpret the results of validation experiments. The confidence intervals are obtained from asymptotically derived likelihood thresholds based on the Chi-squared distribution applied to profile likelihoods. After introducing these concepts using a simply



Question & answer during Andrew Golightly talk.

toy model, Dr. Kreutz then applied these tools to an ODE model of a MAP kinase signal transduction pathway. These results included an observability analysis that showed sufficient data exist to predict the quantities of interest, and suggestions for the particular kinds of measurements that would best calibrate the model. Dr. Kreutz concluded with a summary of these results and the use of these techniques to obtain confidence intervals to use in observability (estimability) analyses.

Thursday

Using Bayesian and MCMC approaches for parameter estimation and model evaluation in physiology

Carson Chow -University of Pittsburg & Laboratory of Biological Modeling, NIDDK, NIH

Search for the "best" model to capture relevant features of a given dataset needs to balance goodness of fit with complexity. Given a dataset there may be multiple competing models available to represent its characteristics. Dr. Carson Chow introduced the idea of using the ubiquitous Bayesian approach for model comparison, and parameter estimation. He shows that ratio of the posterior densities $P(M_2/D) : P(M_1/D)$ (the odds ratio) quantifies comparison for two competing models. This ratio, expressed using the Bayes' rule, requires computation of an integral over a high-dimensional parameter space, and evaluating the maximum likelihood function with respect to the parameter variable. He argues that Bayesian model comparison automatically evaluates models by rewarding fit to the data while penalizing the number of parameters (i.e. complexity). In particular, the Bayes information criterion and Akaike information criterion provides a methodology for model comparison, with a certain caveat that these formulae are valid provided posterior densities are near normal. He next expanded on the method required to integrate over the high-dimensional parameter space by using the approach of thermodynamic averaging, and simulating using MCMC technique at multiple temperatures (e.g., parallel tempering). Dr. Chow presented an application of model comparison to physiology via the example of Insulin's effect on free fatty acids (FFA). With an objective to quantify FFA suppression due to insulin, he presented ODE models for FFA-Glucose concentration and showed comparison results for various models in the literature. Other applications presented in the talk were models to predict insulin secretion rate, and reverse

transition between different states of differentiating embryonic stem cells.

Particle MCMC for Stochastic Kinetic Models

Andrew Golightly -Newcastle University

Description of complex biological reaction networks using mathematical models are useful in developing a quantitative understanding of the process, and testing hypothesis for the reaction mechanisms. Dynamics of biochemical networks exhibit stochasticity, and theory of stochastic chemical kinetics allows description of these network dynamics by a Markov Jump process (MJP). Such processes may be simulated using the Gillespie algorithm, however, inference of the rate parameters is challenging, especially given the imperfect time series observations. Dr. Andrew Golightly presented the recently proposed Particle MCMC algorithms applied to parameter inference problem for the Markov jump process models. Two toy examples, namely, the Lotka-Volterra ODE model for predator-prey dynamics, and the model for prokaryotic auto-regulation, were then presented. Inference for the parameters governing MJP is carried out assuming latency of the true jump process. Then, for Bayesian inference of rate constant parameters, he uses a combination of the Particle MCMC technique, and a vanilla particle filter to estimate conditional density of the latent variable. This approach is computationally expensive and, therefore, he proposes a diffusion approximation (Chemical Langevin Equation) to MJP. Diffusion approximation improves tractability of the problem and, further, the structure of the SDE models is exploited to develop algorithms which are computationally efficient. Inference problem for diffusion processes requires using the Euler-Maruyama scheme to obtain Gaussian approximations to the transition density. Performance of the particle MCMC scheme and the particle filter is improved by considering the "modified diffusion bridge" (Durham & Gallant, 2002) for discretization in the weighted resampling procedure. He then applied this method to two examples and concluded his talk with a proposal to explore certain issues, for instance, appropriate bridge construct (Lindstrom, Linear noise approximation, etc.) for sparsely observed processes, and exploring differential geometric notions in efficient parameter inference.

Summary statistics for ABC model choice

Dennis Prangle -Lancaster University

Dr. Dennis Prangle motivated his presentation with an application to study of demographic history of bacteria *Campylobacter jejuni*. This bacteria is known to be a major cause of gastroenteritis, is hosted by animals, and can spread to humans. The study focuses on New Zealand, and through his work Dr. Prangle wants to address various questions, in particular, if the bacterial population has been growing since European colonization, or earlier, and identify growth rates in livestock/poultry. This, he indicated, will help understand the potential future evolution and response to control strategies. The statistical inference problem in this study deals with model choice given various competing coalescent models, and with testing hypothesis of exponential growth versus no growth. He presented the idea of likelihood-free inference (for instance, approximate Bayesian computation (ABC)) for model selection. The basic principle of likelihood-free idea is that one runs simulations from competing models and base inference on frequency of good matches with the observed data. He described the ABC rejection sampling for model choice, given as an iterative method to obtain accurate estimates of an arbitrary fixed vector of summary statistics. He then remarked on the pros and cons of this methodology, mainly that the results are not robust to summary statistic choice, and proposed a method (Semi-automatic ABC) which addresses some of the disadvantages associated to classical ABC algorithms. The new algorithm provides a method to choose ABC summary statistic for parameter inference and model choice. Application of this method to MLST data from humans, poultry, environment, livestock, and wildlife sources, provides evidence against growth model.

Bayesian inference for generalized stochastic population growth models with application to aphids

Colin Gillespie -Newcastle University

Dr. Gillespie analyzed the effects of various treatments on cotton aphids *Aphis gossypii*. An integrated stochastic model was used to capture intrinsic stochasticity. This new approach allows people to explicitly explore and more accurately assess treatment interactions. Markov chain Monte Carlo methods and the moment closure techniques were used within a Bayesian framework to integrate over uncertainty associated with the unobserved cumulative population size. These methods

were applied to data on aphid counts in the Texas High Plains obtained for three different levels of irrigation water, nitrogen fertilizer, and block. The methods are applicable to a wide range of problems in population ecology.

Linking systems biology models to data: a stochastic kinetic model of p53 oscillations

Richard Boys -Newcastle University

Dr. Boys discussed the assessment and refinement of a dynamic stochastic process model of the cellular response to DNA damage, which is a complex nonlinear continuous time latent stochastic process. The primary goal is to "calibrate" the model by finding parameters of the model that are most consistent with the experimental data. It is therefore most natural to consider a Bayesian analysis of the problem, using sophisticated MCMC methods to overcome the formidable computational challenges, and the model is compared to time course data on the levels of two key proteins involved in this response, captured at the level of individual cells in a human cancer cell line.

Bayesian Modeling of Smoking Exposure During Pregnancy

Vanja Dukic -University of Colorado-Boulder, Canada

Dr. Dukic studied the effects of prenatal exposure to cigarettes, which frequently acquire both self-report and biologic assays of maternal smoking, which are commonly those of cotinine, a metabolite of nicotine, from urine or serum. Both of the measures have their own sources of information and bias. Single bioassay measures alone cannot reflect the metabolic mechanism over time, while self-report may have serious recall, topographic, and metabolic biases. The speaker presented a Bayesian statistical model for describing in utero smoking exposure based on the combined biological and self-report information, and the model takes into account heterogeneity among women and metabolism during pregnancy. The data in the research are from East Boston Family Study.

Friday

Parameter estimation for bursting neural models

Joe Tien -The Ohio State University

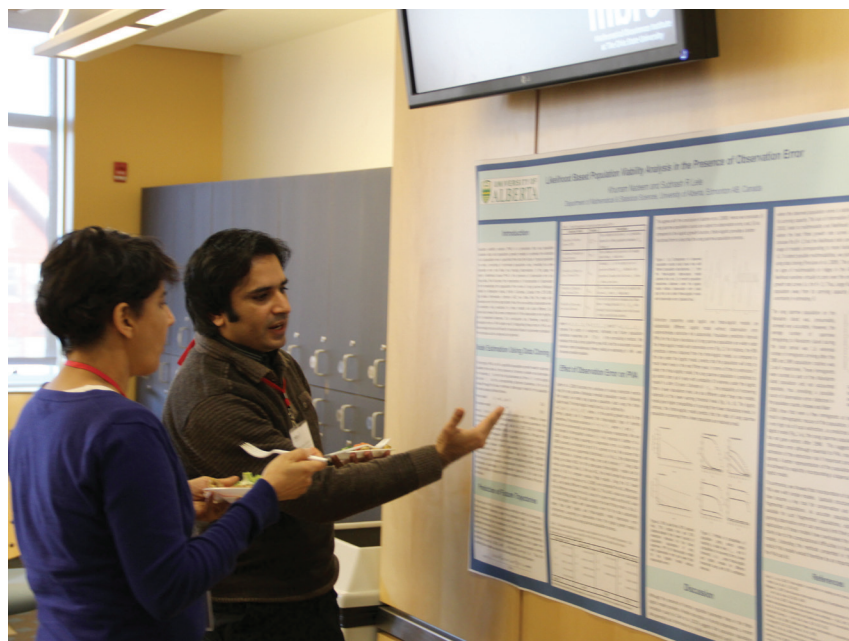
Dr. Tien emphasized on the role of geometry of dynamical systems in guiding parameter estimation. Neuronal burst data reflects specific qualitative characteristics

occurring at multiple time scales. Under certain conditions neurons may exhibit the phenomenon of bursting; that is, there are long periods of quiescence are interrupted by rapid firing of several spikes and a subsequent return to the quiescent state. Standard parameter estimation techniques for these models are unsuitable due to complicated objective function landscapes that make numerical computation a challenging task. Thus, he proposed using geometric properties of the trajectories, for instance, periodic orbits, and geometric definition of bursting to deal with the difficulties of fitting burst data. He illustrated this issue by introducing the Hodgkin-Huxley model (for bursting in respiratory neurons), and presented a generic parameter estimation approach based on the geometric ideas. He showed that matching the key characteristics of the burst data to the model, in particular, the burst events, leads to a simpler objective function landscape. Following the description of the general optimization framework, two applications were presented, namely, Respiration (preBotzinger complex), and Olfaction (External Tufted cells). A few directions to be pursued in the future includes, a more effective way to deal with the boundaries of the feasible region, to establish objective functions which closely capture the details of bursting, inference of geometric features from empirical data, and analyzing the statistical properties of the estimators.

Modeling gene expression changes in cancer with supervised learning

Christina Leslie -Memorial Sloan-Kettering Cancer Center

The primary goal of the study presented in this talk was to dissect mechanisms of regulation of gene expression and dysregulation in cancer using genome-wide transcript level data. The main tools for this study include data-driven models that use machine learning principles to analyze the regulatory mechanism by formulating a prediction problem. Two aspects of the study are crucial, firstly, statistical, i.e. training models that can predict new/held-out experimental data, and secondly, the



biological aspect, which is to shed light on mechanism and extract actionable information. In particular, an application for identifying regulatory subtypes in glioblastoma was presented. Large-scale cancer genomics projects are profiling tumors at multiple molecular layers, including copy number, mRNA and miRNA expression, but the mechanistic relationships between these layers are often excluded from the computational models. Dr. Leslie presented an approach, based on a sparse regression framework (Lasso regression), for integrating molecular profiles to reveal mechanisms of dysregulation of gene expression in cancer, including miRNA-mediated expression changes. Results were presented from application of the approach to 320 glioblastoma tumors, in particular, key miRNAs and transcription factors were identified as common or subtype-specific regulators. Additionally, recent study on the role of stromal cells in the tumor microenvironment was also presented. Stromal cells play a role in tumor progression, for instance, expression changes may come from recruitment to the tumor microenvironment or communication between stroma/tumor cells. Analysis was performed on the HUMU protein microarray data. The object of the study is to develop a model to predict stromal expression changes from tumor expression changes or vice-versa, in particular, using the partial least squares regression for a reduced representation of the data.

Tissue Engineering and Regenerative Medicine

April 30-May 4, 2012

Organizers: Keith Gooch, Doug Kniss, Anita Layton, Chandan Sen, and Qi Wang

Report by: Casey Diekman, Harsh Jain, and Elissa Schwartz

Monday

Engineered skin: New strategies for biomechanical mimicry

Heather Powell- The Ohio State University

Dr. Powell's work on engineered skin is mostly focused on bridging the gap between basic science and translational medicine. Engineered tissues must reproduce the biological and mechanical function of their native counterparts if they are to provide health benefits to society. However, the current generation of engineered skin (ES) fails to match the mechanical properties of native skin, limiting its use in vivo. This is due, in part, to the static, non-physiological conditions used during synthesis. Using mechanical stimuli during tissue culture is known to improve function and strength in engineered tissues. However, this advance has not been fully realized in skin or other complex, hierarchical tissues

with multiple cell lineages and extracellular environments. Dr. Powell's presentation focused on the use of novel mechanical-bioreactor technology in conjunction with materials processing techniques, computational modeling, and biological tools to understand the role of scaffold mechanics, stress gradients, and cell communication during mechanical stimulation of engineered skin.

Simulating the mechanical response of fibrous scaffolds for tissue engineering

Peter Anderson- The Ohio State University

Dr. Anderson's talk was focused on his team's efforts in simulating the response of fibrous scaffolds for tissue engineering. His work was motivated by the use of scaffolds in tissue engineering, such as engineered skin grafts, where mechanical properties of the scaffold plays a critical role in the success of the transplant. With

a view to quantifying local fiber stress-strain behavior, fiber density, and undulations in fiber orientation that provide variations in local stiffness and anisotropy, and which cannot be measured via macroscopic testing alone, his group adopted a combined computational-experimental approach where finite element simulations of electrospun scaffolds were used to link macroscopic stress-strain responses to the underlying fiber geometry and the stress-strain response in individual fibers. Emphasizing the need for incorporating nonlinearities caused by strain stiffening in models of fibrous scaffolds, Dr. Ander-



son presented his model that simulates 54 fibers using a commercially available software – ABAQUS, which admits actual fiber geometries obtained from high-resolution confocal microscopy images and macroscopic stress-strain data as input, and provides as output the local fiber stress-strain response. His simulations underscored the highly non-uniform and anisotropic nature of deformations in fibrous scaffolds, and highlighted the need to account for these in models. They also revealed the scale-dependent nature of mechanical response. Dr. Anderson concluded his talk by mentioning some of the challenges faced the modeling community including scaling up models to large scale images and the long times involved in simulating such nonlinear systems.

Overview of wound healing

Robert Diegelmann- Virginia Commonwealth University

Dr. Diegelmann gave a comprehensive overview of wound healing, during the course of which he pointed out various challenges that face the modeling community working in this area. Dr. Diegelmann began with outlining the various possible responses of the body to an injury. Of these, regeneration is ideal since this entails exact replacement of injured tissue, while what is typically seen clinically is normal wound healing. However, two major problems of abnormal wound-healing are excessive healing, characterized by fibrosis and contractures, or deficient healing, characterized by chronic ulcers. He then outlined the various processes involved in healing, focusing in particular on the various cellular and biochemical signals needed to repair injuries. He emphasized the need for any model of wound healing to accurately capture the four chronic phases of normal healing: hemostasis followed by inflammation, proliferation and finally, remodeling.

Dr. Diegelmann next spoke about the intensive research that has gone into studying abnormal wound healing over that past few years; however, attempts to accelerate or improve wound healing have been largely unsuccessful. He emphasized the need for an integrated systems biology approach to critical injury using physiological data in order to make further progress in improving healing outcomes in patients. In particular, his lab has developed a technique wherein PTFE tubes are inserted in human wounds allowing for the collection of genomics, proteomics, lipidomics, and molecular marker data from healing tissue that can then be fed

into a computational model developed by his collaborators, improving its predictive accuracy and thereby allowing for the testing of novel therapeutic strategies aimed at improving abnormal wound healing.

Multiscale computational and experimental approaches to harness the regenerative power of the periosteum

Melissa Knothe Tate- Case Western Reserve University

Dr. Knothe Tate's work on the periosteum (a sock-like sheath on the outer surface of the bone) spans basic science to product development. The periosteum is a composite tissue that provides a niche for stem cells and exhibits a remarkable regenerative capacity to generate bone de novo within critical sized defects, even in the absence of the medullary cavity (e.g., when it is filled by an intramedullary nail for mechanical stabilization after tumor resection). Clinical reports and recent experiments indicate that mechanical loading enhances the regenerative capacity of the periosteum. Furthermore, implementation of directional delivery implants designed as periosteum substitutes show that periosteum-derived cells as well as other biologic factors intrinsic to periosteum play a key role for infilling of critical sized defects. Dr. Knothe Tate's talk reviewed the mechanobiological factors shown to promote emergence of anisotropic structure and function by stem cells, to facilitate de novo tissue building by periosteum derived cells, as well as surgical and engineering approaches to unleash the power of the periosteum for tissue engineering as well as trauma and reconstruction surgery.

Directed differentiation of stem cells using lasers

Praveen Arany- Harvard University

Dr. Arany presented an application of power lasers as an innovative tool for clinical regenerative applications. His work was motivated by observations in his dental clinic, wherein patients who came in for tooth extractions were treated with low powered laser therapy at the extraction wound sites. Measurements of wound healing parameters including angiogenesis, inflammatory infiltrate, and collagen architecture indicated that laser therapy enhanced wound healing. In particular, this was found to be a result of TGF- β activation as a consequence of laser therapy. Dr. Arany next described how these observations motivated in vitro and in vivo studies where a wide range of analytical techniques were used to demonstrate that low powered lasers mediated TGF- β activation via reactive oxygen species. He concluded



his talk by presenting a potential clinical application of this work. Since TGB-b modulates the repair of dentin, a vital component of our teeth, Dr. Arany proposed that low powered lasers can be used to induce directed differentiation of dental stem cells into odontoblasts, which subsequently leads to dentin formation. This idea is currently in the stages of testing and validation in in vitro and in vivo assays.

Measurement, modeling and rational modulation of inflammation and wound healing

Yoram Vodovotz- University of Pittsburgh

The focus of Dr. Vodovotz's talk was his computational models of the inflammatory response to tissue injury. He began with a short overview of the various challenges that the community of systems biologists faces in modeling real world problems with a view to having a direct and significant translational impact, and described how the overarching goal of his work is to achieve programmable control over the process of inflammation. The rest of his talk was focused on his work on modeling how inflammation feeds into the wound healing process in diabetic foot ulcers and post-spinal cord injury ulcers. Using data-driven and mechanistic agent-based

modeling based on LuminexTM datasets Dr. Vodovotz hypothesized that acute inflammation goes awry when the positive feedback loop of inflammation leading to tissue damage/dysfunction that results in further inflammation, driven by damage-associated molecular pattern molecules, fails to resolve under the influence of anti-inflammatory/pro-healing mediators. In particular, he focused on the role of TGF β and TNF in modulating this process. He then briefly introduced free software for multi-scale agent based modeling called SPARK, and presented several applications of it, including to a model of the vascular epithelium that can account for stresses and oxygen gradients, and thus be applied to studying pressure ulcers and their treatment. He also presented a model of blood vessel injury due to angioplasty that was also simulated using SPARK, highlighting its broad applicability. Dr. Vodovotz concluded by summarizing his group's approach to improving wound healing, which entailed the measurement or discernment of patterns in wound images that are then fed into mechanistic models. Various therapies may be easily tested on such validated models resulting in the rational modulation or reprogramming of inflammation in order to achieve optimal therapeutic results.

Tuesday

Matrix stiffness and cell behavior

Valerie Weaver- University of California, San Francisco

Dr. Weaver's group studies cancer as well as development. The main theme her lab is working on is the interplay between cell and tissue force as tissues transform and metastasize in skin, breast, brain, and pancreatic cancers. It is well known that tumors are stiffer than normal tissue, and recently Dr. Weaver's group has shown that it is the extracellular matrix (ECM) that stiffens in tumors. Increased matrix stiffness has a number of effects: it disrupts morphogenesis, promotes focal adhesion maturation, and enhances adhesion signaling. Dr. Weaver's talk focused on her work with integrin signaling. The take-home message was that in certain types of cancers, both extrinsic changes such as ECM remodeling as well as intrinsic changes in oncogenes drive up cell tension, which modifies integrin signaling and influences cell behavior.

Long-range mechanical forces enables scaffold-free self-assembly of epithelial tubules

Chinlin Guo- California Institute of Technology

The underlying theme of Dr. Guo's talk was applying the principles of cell-microenvironmental self-assembly in the construction of large-scale cellular functional devices. As an illustration of this principle, he described experiments that showed how acini change morphology to develop linear patterns in response to type I collagen in the ECM, due to the transmission of cell-generated mechanical forces over long ranges by the collagen. As an extension of this, he demonstrated how micro-patterned scaffolds could be used to control linear pattern self-organization in these acini. The main thrust of Dr. Guo's presentation was to answer the question "can unbranched long tubules of length > 1 cm self-organize through cell-ECM interactions?" Currently, this is only possible on premade scaffolds. Remarkably, he showed that adult epithelial cells and type I collagen molecules can self-assemble into centimeter-long, hundred micrometer-wide and un-branched tubules under scaffold-free conditions. The self-assembly was found to require cell-collagen interactions in the liquid phase and in contrast with conventional thoughts, the initial template formation is primarily mediated by long-range (~600 micrometers) mechanical interactions rather than gradients of soluble factors between cells. This mechanism was further confirmed by a simple calculation of the free energies of the tubular structures. Furthermore, the ability of cells to form tubules depended on initial and boundary conditions of the culturing systems, with stability of the linear templates an increasing function of their lengths. Dr. Guo concluded his talk by mentioning a few applications of his work to modulating myofibril/vascular tubule self-organization, as well as improving wound-healing by long-range mechanical coordination.

Strain confinement in non-linear biological media

Leonard Sander- University of Michigan

Dr. Sander's talk was about the micromechanics of nonlinear biological polymers. Such mechanics are important in a lot of areas of biology, including the pulling together of collagen by fibroblasts during certain stages of wound healing. Collagen and most biopolymers have

non-linear elasticity, and fibers align at large strains; this leads to strain-stiffening. Since alignment only occurs at large strain, it will be confined to a region very near the cell. Thus, in non-linear, strain stiffening biopolymers, localized sources of strain can give rise to local alignment and large strain out to a certain radius, and very small strain outside. Dr. Sander's gave evidence for this effect and estimated the 'horizon' for strain propagation.

Continuum approximations of cell-based models of bacterial chemotaxis

Chuan Xue- The Ohio State University

Dr. Xue presented her cell-based models of bacterial chemotaxis, which integrate high level details of fundamental cellular mechanisms and can reproduce several experimentally observed bacterial patterns. Her models were motivated by an enteric bacterium which forms a variety of spatial patterns such as radial and spiral streams in colonies. She began with a detailed overview into how bacterial cells move, using their flagella to generate a 'run and tumble' motion that is characterized by



Victor Barocas

two time scales: excitation (fast) and adaptation (slow) in response to chemotactic cues. Using a hybrid model, where cells are treated as agents, chemoattractants as a continuum and ODEs used to simulate intracellular signal transduction that can capture the two time-scales, Dr. Xue showed that the observed radial streams in bacterial colonies result from the modulation of the local attractant concentration by the cells, and that the chirality of the spiral streams resulted from a swimming bias of the cells near the surface of the substrate, thus providing mechanistic insight into pattern formation in bacterial colonies.

In the second part of her talk, Dr. Xue showed how continuum PDE models could be derived from her cell based models using asymptotic methods. In particular, she showed how her cell-based model reduces to a modified version of the classical Keller-Segel equation and the (macroscopic) chemotactic sensitivity function thus obtained is easily interpreted in terms of microscopic parameters from the hybrid model. To allow for time-dependant signals, and to incorporate the effect of hydrodynamic forces that arise when cells swim close to the surface required the development of a new approach to solving the moment equations that arise from the transport equation that does not involve closure assumptions. Dr. Xue concluded with some future directions of her work, including applying her methods to understanding amoeboid chemotaxis.

Mechanical control of spheroid growth: Distinct morphogenetic regimes

Sharon Lubkin- North Carolina State University

Dr. Lubkin addressed the question of what drives morphogenesis. She presented a mixture model of transport and growth in epithelio-mesenchymal interactions. The model was parameterized and her analysis showed that sustained growth required bulk growth, surface growth, and capsule formation, leading to complete growth arrest. The model revealed a bifurcation delineating bulk growth from growth arrested by capsule formation in the mesenchyme. The bifurcation is determined by just two ratios that matter: the relative strength of epithelial growth and that of proteolytic activity (i.e. the mesenchymal removal rate). The model provides a theoretical basis for explaining observations of growth arrest despite proteolysis of surrounding tissue. She pointed out that growth can be sped up with

growth factors, but too many growth factors will halt growth due to capsular growth arrest. Her model also provided a quantitative framework for the design and interpretation of experiments involving spheroids and tissues, which are locally equivalent to spheroids. The results offered guidance for optimizing the production of replacement tissue from spheroids.

Modeling cell-cell and cell-extracellular matrix interactions with random switching terms

John Dallan- Brigham Young University

Dr. Dallan focused on identifying the important factors in collagen alignment in order to more fully understand the process of wound healing. In wound healing, various cell types are recruited to the wound region to repair the wound. More specifically the collective motion of epithelial cells is required to repair a defect in the tissue layer as cells migrate into the wound region restoring the integrity of the epidermis. Thus modeling cell-cell and cell-extracellular interactions is fundamental in order to alter, predict, and ultimately control wound healing. These cell-cell and cell-extracellular interactions are both force and biochemically based and are mediated by random processes. He modeled the force interactions as a system of differential equations representing the location of the cell centers and their surrounding interaction sites, using terms linking the different equations to represent random interactions between the sites. The model can be used to determine, for example, that less TGF- β decreases scarring, whereas more TGF- β increases scarring. He presented several simulations of wound healing showing the factors that influence the alignment of collagen.

Wednesday

Multiscale models of collagenous materials

Victor Barocas- University of Minnesota

The focus of Dr. Barocas's talk was to present his experimental-driven multiscale models of collagenous materials that incorporate micro-structural information into a macroscopic description of the material. Briefly, a finite element mesh was used to model the macroscopic scale, while a network model comprising 500 fibers, each of which is represented by a fiber constitutive equation, was used to scale down to the microscopic level. His model was based on experiments where fibroblasts entrapped in cross-shaped fibrin gels were



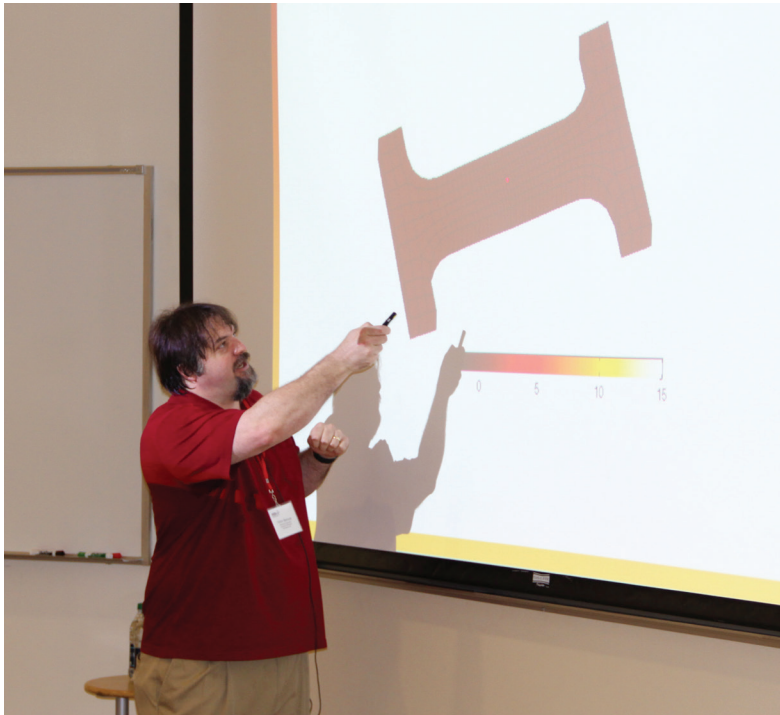
Robert Diegelman

studied to assess how the tension and alignment of cells affected ECM deposition. He next demonstrated how the scope of his model could be expanded to investigate how the co-gelation of collagen and fibrin affects the properties of each individual protein network. The model predicted a decrease in mean fiber diameter for both proteins, accompanied by an increased failure strain and high connectivities for collagen gels.

The second part of Dr. Barocas' talk was focused on modeling the failure of individual fibers of collagen, and interpreting what this means for the macroscopic properties of the network. To simulate failure, his earlier model was modified to include a critical stretch parameter, and the model rigorously fit to experimental data. The model also did a good job in predicting fiber align-

ment observed under polarized light microscopy at the site of failure.

Dr. Barocas then continued in a third direction, presenting some current work, where collagen-agarose co-gels are used to study the role of non-fibrillar matrix (NFM) as a component of soft connective tissues. Voronoi networks were used to represent collagen fibers and the NFM assumed to be a neo-Hookean solid. Once again, model predictions of total stress and Poisson ratios matched experimental observations closely, and the model could be reliably used to elucidate the interaction between collagen and NFM in uniaxial tension.



Victor Barocas

Multiscale computational simulations of fiber remodeling and cell compaction in collagen gels

Ed Sander- University of Iowa

Dr. Sander's work is to try to understand the complex relationships between microstructure, the heterogeneity of tissues, and the resulting functional properties of tissues. The goal is to develop predictive models for how tissues grow and adapt in response to mechanical stimulation. Multiscale mechanical interactions are scale spanning physical interactions between the tissue and the extracellular matrix (ECM). They are involved in a variety of biological phenomena, including tissue growth, remodeling, disease, and damage. These interactions are important to characterize because they control both the mechanical behavior of the tissue and the manner in which mechanical signals are propagated to the cellular level. Dr. Sander's talk discussed recent work incorporating (1) fiber-level rules that govern enzymatic degradation and growth and (2) contractile elements that simulate cell compaction and a redistribution of forces within the surrounding fiber networks into their multiscale modeling framework. Understanding the role of these processes is crucial to comprehending and controlling the integrated response of the mechani-

cal environment in a number of biological contexts.

Adipose TE: The matrix matters

Torsten Blunk- University of Wurzburg

Adipose tissue engineering (TE) has the potential to cater for the tremendous clinical need for adequate implants required for the repair of soft tissue defects resulting from tumor resection, traumatic injury or congenital anomalies. Currently used materials such as silicone and collagen suffer from major drawbacks including foreign body reaction and migration of the implants. On the other hand autologous adipose tissue creates donor site defects and is susceptible to necrosis, highlighting the need for adipose TE, wherein adipose stem cells are harvested from the patient and developed ex vivo into implantable constructs. In his talk, Dr. Blunk presented some recent work carried out in his lab in the field of adipose TE. He began by presenting some early work in this field, where he used a scaffold-based adipogenesis

model to develop coherent 3-D adipose tissue constructs in long-term culture. The in vivo transplantability of these constructs was found to be crucially dependent on their precultivation. He then presented a broader review of the role of various cells in adipose TE. Dr. Blunk highlighted the vital role of ECM in the construction of such implants. For instance, long-term studies carried out in his lab suggest that enzymatically degradable hydrogels promote the formation of coherent adipose tissue-like structures. In fact, hydrogels functionalized with a laminin-derived adhesion peptide demonstrated significantly enhanced adipogenesis as compared to controls. Dr. Blunk also mentioned some on-going work in his lab where the effect of altering the surface chemistry properties such as cell adhesiveness of polymer gels on preadipocyte differentiation, and hence adipose tissue construct functionality, is being investigated.

Dr. Blunk concluded by presenting some 3D spheroid models his lab is developing that would allow for significant advances in basic research of adipose TE such as elucidating how cell-cell and cell-ECM interactions influence adipogenesis and the endocrine function of

adipose tissue. These models also have an advantage over conventional 2D cultures in that they better reflect the physiological tissue. To demonstrate their applicability, Dr. Blunk showed how these 3D models were used to explicate role of prolyl-4-hydroxylase in regulating adipogenesis, which was not possible in 2D cultures. His current work includes using the 3D model to investigate the role of ECM and angiogenesis in adipogenesis, as well as to develop 3D implants.

Computational modeling of cartilage regeneration

Sarah Olson- Worcester Polytechnic Institute

Dr. Olson's talk was on mathematical models she has

developed for cartilage tissue engineering. Articular cartilage is a connective tissue lining bony surfaces in diarthrodial joints (knees, hips, and shoulders). When degradation exceeds the synthesis of extracellular matrix constituents, cartilage will start eroding and fragmenting, eventually leading to defects. Since cartilage has a limited capacity for growth and repair, defects due to osteoarthritis and injury may rapidly progress to complete tissue degradation, necessitating a joint replacement. Prior to complete tissue degradation, defects could be filled with cell-seeded biocompatible porous scaffolds, with the hopes of repairing and regenerating new



Sharon Lubkin

tissue. In order to achieve biological and mechanical functionality of these constructs, many factors need to be considered. Dr. Olson's talk highlighted key aspects such as nutrient transport, cell proliferation and migration, matrix synthesis, and mechanical interactions in the context of cartilage regeneration. Previous computational work was described that ranged from the use of neural networks, reaction diffusion models, level set methods, and continuum modeling frameworks to investigate and understand aspects of cartilage tissue engineering.

Interplay between active and passive mechanical forces in microvascular network formation

Alisha Sarang-Sieminski- Franklin W Olin College of Engineering

Dr. Sarang-Sieminski presented work using an in vitro model of microvascular network (MVN) formation to investigate how matrix properties influence cell behavior. Specifically, she examined the interplay between the mechanical properties of the matrix (passive) and cell force generation (active). She modified the collagen matrix stiffness to determine the relationship between cell traction and matrix stiffness. Among the results presented, she showed that the gathering of matrix

around cells precedes cell elongation and MVN formation and decreases as a function of increasing cell-cell distance and collagen stiffness. She also showed that the patterns of matrix gathering are consistent with the hypothesis that nearby cells form lines of matrix tension or alignment that they elongate along in order to form multi-cellular structures. This work adds to our understanding of MVN formation at the cellular length scale as well as the role of cell-derived forces and matrix remodeling in differentiated cell functions. The findings presented have implications to cell and developmental biology, wound healing, tumor formation, and the design of new tissue engineering scaffolds.

Extracellular matrix fibers and stress transmission between cells

Richard T. Hart- The Ohio State University

The aim of Dr. Hart's talk was to investigate whether the fibers in the extracellular matrix (ECM), or the strain-hardening behavior of the ECM, play the key role in transmitting long-range mechanical signals between fibroblast cells. He used finite element models and confocal reflectance microscopy to compare how far stress signals are propagated in fibroblast-seeded collagen gels. He analyzed models that include the gel's fibers as well as homogenous linear-elastic and strain-hardening models. He showed that stresses are propagated farther in a fibrous matrix as compared to linear elastic or strain-hardening homogenous materials. His results



support the hypothesis that ECM fibers play the key role in long-range stress transmission, and that strain-hardening effects are secondary. These results help inform our understanding of how cells are able to communicate via mechanical signaling.

Mathematical and computational modeling of cell-matrix interactions

Keith Gooch- The Ohio State University

Dr. Gooch is primarily an experimentalist, but in this talk discussed some of his mathematical and computational work modeling cell-matrix interactions at different length scales. He first discussed cell-mediated compac-

tion of ECM, and phenomenon that was pointed out in some of the very first papers on tissue engineering. He posed the question "what causes the gel to stop compacting?" and suggested two hypotheses: (1) the cells are forced or decide to stop pulling or (2) the cell keeps pulling or but the resistance of the gel prevents further compaction. However, experimental data and continuum modeling excluded both of these hypotheses. So at this point they moved to a different conceptual model that focused on peri-cellular values, not global averages. This is motivated by the fact that cells are discrete and collagen bundles around cells, so on the cellular length scale there is a strong gradient and just looking at average values of collagen might be deceptive. The conceptual model and some simple derivations gave a nice mathematical explanation why final collagen

concentration is a counterintuitive function of initial collagen concentration. The model favors the hypothesis: Once a target pericellular value has been reached, the cells no longer pulling regulate the degree of cell compaction.

Dr. Gooch then moved on to discuss his use of agent-based modeling to explore cell-matrix interactions. His goal here was a qualitative model to explore the relationships between potentially important players and outcomes of interests. Agent-based models were developed where cells and ECM fibers are each considered as systems of multiple interacting agents. In these models, the physical properties of cell and fibers are based on a set of conceptually reasonable mechanical processes and the dynamics of cell-matrix binding and unbinding are considered as simple position- and strain-dependent processes. From these relatively simple sets of rules, complex behaviors arise that are consistent with experimental data including cell-mediated compaction of ECM fiber networks, the alignment of ECM fibers between cells, and the directed migration of pairs of cells towards one another. In addition, there is evidence consistent with durotaxis and haptotaxis arising as emergent behaviors from these simple sets of rules. The implications of the peri-cellular distribution of ECM predicted in these agent-based models and observed experimentally were

explored in a mathematical model of cell-mediated compaction of ECM.

Mathematical analysis of traction force microscopy: Influence of cell mechanics, adhesion and morphology

Samir Ghadiali- The Ohio State University

Dr. Ghadiali's talk was about the technique of Traction Force Microscopy or TFM, focusing on what it actually measures and why researchers need to be more careful with it. TFM is commonly used to assess the contractile properties of cells. The generation of contractile forces is essential to numerous biological and pathological processes including development, growth, wound healing, and cancer cell migration/invasion. In TFM, the displacements of fluorescently labeled beads embedded into the ECM or substrate are measured and converted into a traction stress field using inverse analytical or finite element methods. Recently, standard 2D TFM methods have been extended into 3D and the traction stress field generally used as a measure of cell contractility. However, Dr. Ghadiali's lab hypothesized that changes in several biomechanical and morphological properties (i.e. cell stiffness, cell-substrate adhesion and aspect ratio) may alter the traction stress field measured by TFM. The fact that multiple parameters other than contractility can influence TFM measurements may lead to inappropriate interpretation of experimental results. Therefore, they have developed an idealized finite element model of 2D and 3D TFM and have used this model to evaluate how cell mechanical and morphological properties influence TFM measurements. Results indicate that even for equivalent contractile stress, changes in cell stiffness (Young's Modulus) and adhesion energy can lead to dramatic changes in the contractility as determined by TFM. These results therefore indicate that in addition to TFM, several other biomechanical measurements of stiffness and adhesion are required to appropriately interpret TFM measurements and assess changes in cell contractility.

Thursday

Cell-matrix interactions in TE heart valve

Michael Sacks- University of Texas, Austin

Dr. Sacks' discussed scaffold-matrix interactions in engineered valvular tissues. He focused first on heart valve biomechanics, including structure-based models, microstructure (i.e. why there are multiple layers),

and the cell level. He then discussed engineered tissue approaches, including congenital defects of the heart. His computational model of stress, strain, and scaffold geometry reproduced what was seen in the experimental data. Next he estimated the postnatal growth deformations in the main pulmonary artery and found nonuniform growth. He examined what mechanisms drive somatic growth and determined that it was not a standard growth nor was it a deviation from homeostatic growth, but rather stress-modulated epigenetic mechanisms that were locally controlled and mechanical in nature.

Towards a complete neuromechanical model of pumping in tubular hearts

Laura Miller- University of North Carolina, Chapel Hill

Dr. Miller's talk explored the question of how intracardial flow patterns change during development. She began by showing a video of a classic experiment demonstrating that flows with low Reynolds number (viscous-dominated) are reversible, but high Reynolds number flows (inertia-dominated) are not. This has implications for heart pumping, as the embryonic heart grows from a viscous-dominated valveless tube into an adult heart, which is an inertia-dominated chambered pump. Recent advancements in computational fluid dynamics have enabled Dr. Miller to efficiently explore problems that involve moving elastic boundaries immersed in fluids for problems such as cardiac fluid dynamics. She has found that the presence of vortices and the magnitude and direction of shear are particularly sensitive to geometry and scale near a Reynolds number of 1. She also described modeling the interaction between a fluid and a neuromechanical model of an elastic organ. The tubular hearts of some ascidians and vertebrate embryos offer a relatively simple model organ for such a study. Blood is driven through the heart by either peristaltic contractions or valveless suction pumping through localized periodic contractions. Models considering only the fluid-structure interaction aspects of these hearts are insufficient to resolve the actual pumping mechanism. The electromechanical model she is developing integrates feedback between the conduction of action potentials, the contraction of muscles, the movement of tissues, and the resulting fluid motion.

Coaxing myogenic stem cells into highly functional engineered tissue

Nenad Bursac- Duke University

Dr. Bursac focused his talk on the role of biomechanics and cell-matrix interactions in force production for skeletal and cardiac muscle tissues, and on his lab's work in functional skeletal and cardiac muscle tissue. Cardiac and skeletal muscle development and regeneration involve complex interactions among different cell types, biochemical and biophysical stimuli, and extracellular matrix molecules. Studies of how each of these components influences the tissue morphogenesis, function, and disease are often precluded by the complex structure of the native tissue and the inability to directly control or monitor cellular processes and fates in vivo. The use of tissue engineering technologies, on the other hand, allows for the generation and manipulation of 3-dimensional cell culture systems to both improve understanding of the myogenic processes in vitro and enable the development of new therapies for heart and muscle disease. Recently, their efforts have been focused on the use of stem cells and natural hydrogels to construct cardio- and myo-mimetic tissue culture systems with enhanced functional output. They find that specific combinations of hydrogel composition, dynamic biochemical culture environment, boundary conditions imposed on cells, and supporting non-myogenic cell types can uniquely advance structural and electromechanical properties of engineered muscle to resemble those found in age-matched tissues in vivo. These studies provide insights into the principles of functional myogenesis that could lead to the development of efficient tissue engineering therapies for human disease.

Alterations in extracellular matrix properties effect cardiac differentiation and cardiomyocyte proliferation

Lauren Black- Tufts University

The goal of Dr. Black's talk was to understand the role of the interactions between single extracellular matrix (ECM) proteins and mechanical stiffness on cell function. This is particularly important, as the ECM is a complex mixture of proteins that change both in composition and stiffness throughout normal development. He investigated the effects of alterations in substrate stiffness and substrate composition on cardiac differentiation of stem cells and cardiomyocyte proliferation, using a polyacrylamide gel system with binding sites generated from solubilized decellularized cardiac ECM.

This system effectively enables the ability to decouple stiffness and composition to investigate their individual roles as well as synergistic or antagonistic effects. He showed that fetal cardiac ECM composition enhances neonatal cardiomyocyte proliferation over adult cardiac ECM. His results are consistent with a paradigm in which hyperplasia (growth by cell proliferation) occurs in the fetal stage, followed by a transition period in the neonatal stage, to growth by hypertrophy (growth by increasing cell size) in the adult stage. He concluded that there is a complex interaction between ECM stiffness and ECM composition governing the cardiac differentiation of mesenchymal stem cells.

Quantification of "actin groups", a new cytoskeletal mechanism of cell-fiber interaction

Nicanor Moldovan- The Ohio State University

Dr. Moldovan focused on interactions between cells and ECM-like scaffolds, which are two primary constituents of many tissue engineering constructs. In the course of studying such implants, he found that when endothelial progenitor cells were used in scaffolds made of polymeric fibers, the cells engaged with the fibers by a novel filamentous (F) actin-rich cytoskeletal structure, in a process he termed 'actin grip'. Interestingly, Focal Adhesions (FA) commonly found in stress fibers, were absent in these grips, indicating the dynamic nature of actin-grips. Given that these grips control attachment of cells to fibers independently of FA, and therefore represent potentially new applications in tissue engineering constructs, it is important to characterize their properties, such as their geometry, their co-localization with signaling molecules, and their impact on cell density and shape within the scaffolds. To this end, Dr. Moldovan described an automatic image analysis program of three dimensional confocal microscopy images, that is currently under development in his lab, and which will provide estimates of these parameters once it has been validated. The algorithm utilizes non-parametric segmentation methods to detect nuclei in 3D stacks, and thus provides a quantification of nuclear density and morphology within the scaffolds. An application of this method is to investigate the distribution of F-actin in capillaries, which could explain the shapes of endothelial cells lining them. Dr. Moldovan concluded his talk by highlighting the usefulness of his work in achieving increased control over cell attachment and detachment to fibrous scaffolds, and possibly of cellular differentiation.

Constrained mixture model of growth and remodeling

Jay Humphrey- Yale University

The primary structural constituents of the arterial wall are elastic fibers, smooth muscle, fibrillar collagens, and glycosaminoglycans. In this talk, Dr. Humphrey explored the individual and coupled contributions of these constituents to arterial homeostasis, modest adaptive remodeling in response to altered blood pressure and flow, and extreme remodeling in abdominal aortic aneurysms, based on both experimental data and computational modeling. He showed that elastic fibers play a fundamental role in allowing optimal adaptations, including important effects on collagen turnover. Similarly, smooth muscle contractility can work together with collagen remodeling to promote favorable adaptations to altered flow and pressure. Loss of elastic fibers and smooth muscle contractility, as in abdominal aortic aneurysms, thus results in a maladaptive remodeling response that nevertheless can be protective for long periods (i.e. years). He also presented results from computational modeling that generate novel hypotheses regarding matrix remodeling, and suggested this should be explored experimentally.

Friday

Computational modeling of myocardial infarct healing

Jeffrey Holmes- University of Virginia

Dr. Holmes' talk concerned the role of mechanics in the healing of myocardial infarcts. In experiments in rats and pigs, he showed that infarcts healing in different mechanical environments develop different collagen fiber structures, mechanical properties, alignments, and scar formations. Thus different mechanics will alter scar structure following myocardial infarction. He then presented an agent-based model of scar formation in order to evaluate the mechanisms by which the mechanical environment directs collagen deposition and remodeling by cardiac fibroblasts. He also aimed to use the model to further understand the effects of therapeutic interventions on evolving scar structure. The model tracked each fibroblast's position, orientation, and speed. Each cell could move, proliferate, and apoptose. All but three of the model parameters were determined independently from data. Model validation showed a great fit of the model to data. He used the model to show (1) the role of mechanics, (2) that pre-existing

matrix was the most important queue in the initial alignment of matrix, (3) that the effect of the infarct shape was not important in the cardiac case, and (4) the role of transmural variation. The computational model of infarct healing can be used to 'knockout' one potential mechanisms at a time to determine its effects. Furthermore it enables in silico screening of novel therapeutics for potential adverse effects on scar formation.

Myofibroblasts in the electromechanical function of TE heart

Elliot Elson- Washington University

Dr. Elson's talk focused on the effects of myofibroblasts on the electrical and mechanical functions of engineered heart tissues. He aimed to understand the effect or pattern of electrical activation in the heart. He examined force and stiffness versus strain, excitation contraction modeling, membrane capacitance and electrophysiology, tension profiles to get cell contraction, twitch forces, and tension measurements grown in 3-D hydrogels. He used computational modeling to simulate infarcts and to eliminate elements of one pathway or another to evaluate the result. Using computation and experiment together, he gained a picture of the overall mechanics. He concluded that it is possible to separate the cell and matrix contributions to the reactive force exerted by a tissue.

Modeling fusion of multicellular aggregates and endothelialization with applications to biofabrication

Qi Wang- University of South Carolina

Dr. Wang discussed a novel biofabrication technology known as bioprinting using multicellular spheroids. In this new technology, tissues, organs, and their vascular supply networks are to be fabricated using the multicellular spheroids as the building blocks in various configurations. Cellular spheroid fusion, endothelial cell motion during fusion, and lumenization are key interesting issues to be studied. He then presented a mathematical model based on phase field theories to model the fusion process and possible cell sorting and endothelialization. Cell-cell interaction via collagen substrates is effectively modeled as a long-range force interaction among the cell aggregates. 2-D and 3-D numerical simulations demonstrated the formation of lumens and various bioconstructs due to fusion of vessels and multicellular spheroids.

Statistics, Geometry, and Combinatorics on Stratified Spaces Arising from Biological Problems

May 21-25, 2012

Organizers: Stephan Huckermann, Huiling Le, Ezra Miller, Megan Owen, and Victor Patrangenu

Report: Arjun Beri, Shu Dai, Sam Handelman

Monday

Some Recent Experience with Clostridium Difficile

Peter Kim - McMaster University

Humans have evolved intimate symbiotic relationships with a consortium of gut microbes, individual variations in the microbiome that influence host health, and affect drug metabolism. Dr. Kim discusses the recent experiences with *Clostridium Difficile* along with fecal therapy as an effective alternative to standard antibiotics. *C. difficile* has become the leading cause of hospital-acquired infections, and an increasing incidence rate has been observed in U.S.A. The failure rate of using the antibiotic metronidazole and vancomycin, in the sense of persistent recurrence of infection has led medical researchers to look for alternative treatment. Alternative treatment is carried out by transplanting stool procured from a healthy donor into infected gut community via colonoscopy, nasogastric tube, or fecal enema. As seen from the statistical data, restoration of indigenous community leads to successful control of the infection.

In the experimental study, post the fecal transplant, 25 out of 27 patients experienced clinical resolution. Five elderly patients needed second transplantation such that three out of five had clinical resolution. Moreover, no relapse or adverse effects were observed in successful transplants. Through the study undertaken by Dr. Kim, he wanted to verify the hypothesis that CDI is characterized by a reduction in microbial diversity due to persistent disruptions by symbiotic misbalance. Deep sequencing of microbial ecology in the gut was utilized to characterize ecological diversity of human intestinal microbiota. A study involved taking fecal samples from patients prior to fecal transplantation and after the treatment. DNA from bacteria in the samples was extracted, and a portion of 16S RNA amplified. He de-

scribed the steps involved in deep sequencing in details, consisting of DNA being suspended in solution, followed by addition of sequence specific primers to solution and polymerization of DNA using heating and cooling procedures. After the data is obtained, a binning procedure is used to assign sequences to operational taxonomical units (OTUs) and principal component analysis is carried out. The result was that 80% of variance was explained by 5 dimensions. Analysis of the extracted DNA data shows various relative abundances of bacteria, for instance, Proteobacteria, and Firmicutes, increase from pre to post fecal transplant.

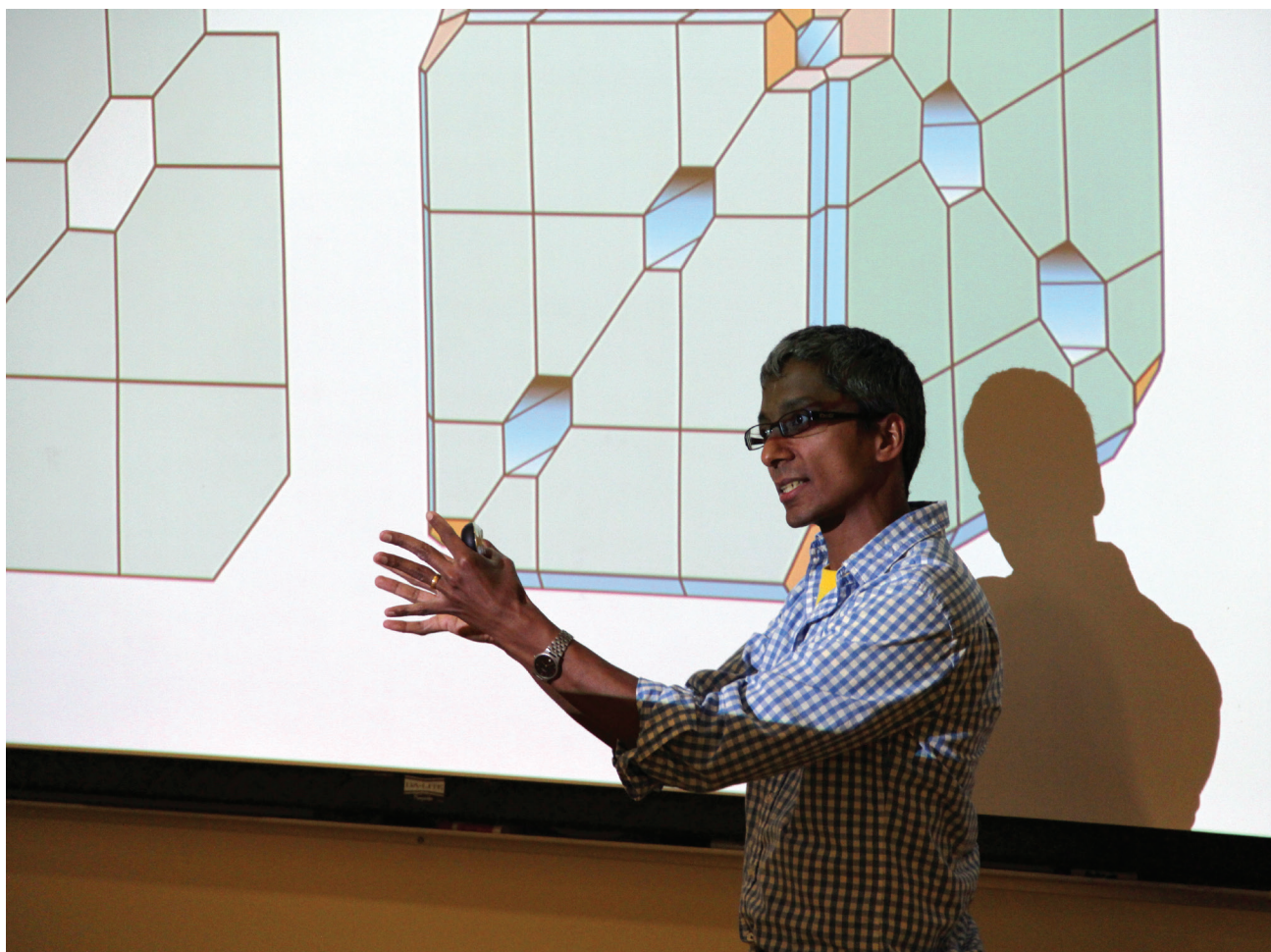
Geometry and Statistics of data

Hongtu Zhu - University of North Carolina

The integration of geometry with statistics began with the field of classical information theory. However, manifold-valued data in neuroimaging, becoming available due to advent of modern medical imaging technology, needs a different approach. Statistical methods for manifold-valued data are currently limited to estimating intrinsic and extrinsic means, estimating the structure of population variability, and for principal geodesic analysis.

Dr. Zhu in his study is trying to understand the relation between the brain function and its anatomical structure by regression analyses of manifold-valued data. For instance, the brain development may depend upon various covariates, in particular, DNA (genetic), environment, age, gender, etc. He described a variety of manifold-valued data occurring in medical imaging, namely, directional data, deformation tensors, diffusion tensors, principal directions, medial representation, projections, orientation, rigid motion, etc. He pointed out the current trends in the field, in particular, his work in medial representation of subcortical structures, analysis of shape data, diffusion tensor quantification of the fiber

Statistics, Geometry, and Combinatorics on Stratified Spaces Arising from Biological Problems



Satyan Devadoss

structure in white matter which leads to the space of symmetric positive diffusion matrices, PDF-valued data obtained from the fiber structure of the brain which is then analyzed using information theory. Another topic is the image registration of multiple images, say, of one 3d image from different angles, Atlas building and longitudinal atlas building of temporal data of brain image. Dr. Zhu pointed out that the objective in studying the brain structure is to obtain knowledge of brain connectivity. This comprises of three critical aspects, anatomical connectivity (anatomical links), functional connectivity (statistical dependence), and effective connectivity (causal influence). Some of the interesting scientific questions pertain to the strength and pattern of the network of brain regions. In his current work, Dr. Zhu is developing an intrinsic regression model for the analyses of the manifold-valued data as responses in Riemannian manifold and their association with a set of covariates.

He explained that he is using a reverse approach to tackle the additional problem of classification of images by inferring the latent space. Other challenges include the question about the high dimensional response prediction, metric selection for regression, and estimating distribution of the manifold-valued data.

Approaching the evolution of novelty: where biology needs math and statistics

David Houle -Florida State University

There are two kinds of novelty in nature, quantitative – phenotypes that are outside the range of normal, but are changes in the mean of the traits that exist, and qualitative – appearance of a feature that is not found in an ancestral species. Dr. Houle, in his experimental study, uses the wing of *Drosophila*, in particular,

Drosophila Melanogaster, as a model to understand the relationship between genotype and complex phenotype, and its effect on evolution. Data considered are the curves defined by the veins on the wings of the insect. There were 54 landmark points considered, which then characterize the shape or topology of veins, and B-splines are utilized to obtain curve fits to these data points. Such data are then analyzed to deduce species variation in shape versus allometric size (quantitative differences) relationship. Variation is important because it controls evolutionary potential. He measures ability to produce quantitative novelty. Moreover, this further provides a measure of capacity to produce and maintain genetic variation capable of allowing an evolutionary response. Dr. Houle explored the question whether one can create novelty by manipulating genes. This, he pointed out, will help in inferring the pattern of effects of mutation, variation, and divergence of wing shape in the genus *Drosophila*.

Medians, means and minimax centers in Riemannian geometry: existence, uniqueness, robustness and algorithms. Application to Signal Detection.

Marc Arnaudon - CNRS

Many data-sets arising in, for example, medical imaging cannot be considered as emanating from vectorial spaces but rather as lying on curve manifolds. Hence, statistics in Riemannian geometry is a crucial area of research. Dr. Arnaudon introduced the notions of mean, median, and minimax centers of a probability measure

on a Riemannian manifold. He illustrated the idea with examples, in particular, the space of real symmetric positive definite matrices with Riemannian metric given in terms of the eigenvalues, and the space of Gaussian processes. Detailed results on the existence and uniqueness for medians, means, and minimax centers of probability measures on Riemannian manifolds, including the case when the probability measure is supported in a regular geodesic ball, and the case of generic data points in a complete manifold. Properties of the Riemannian barycenter or the Karcher mean, and Frechet median of probability measures were also presented. Dr. Arnaudon also discussed the deterministic or stochastic gradient descent algorithms, and showed their convergence. Simulation results of the algorithm were shown in the case of Toeplitz Hermitian positive definite matrices coming from covariance matrices of autoregressive processes.

Tuesday

Towards statistical topology: homology, persistent homology and persistent landscapes

Peter Bubenik - Cleveland State University

It is often advantageous to take local properties of structures or systems or extend or extrapolate from these to the properties of a larger system; or, take the properties of a larger system to predict a range of likely local outcomes. Dr. Bubenik explores this issue in the context of a “nowhere-vanishing continuous tangent vector field,” also known as the “combining a hairy ball problem.” Topological questions of this kind have application in numerous biological problems including those with an obvious topological component (such as protein-ligand docking) and in other more abstract cases. Dr. Bubenik’s approach takes simplicial complexes (which Dr. Bubenik’s approach constructs generically from any set of points in a space) and simplifies the question of dealing with them by studying the homology of the kernel density estimator-filtered simplicial functions, and the persistent homology across different homology degrees/scales. The audience expressed considerable interest in the



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computational complexity associated with various aspects of the approach, driven by the interest in application. Finally, this approach makes it possible to statistics on the homology between point clouds, when treated in this way.

Statistics in Tree Space

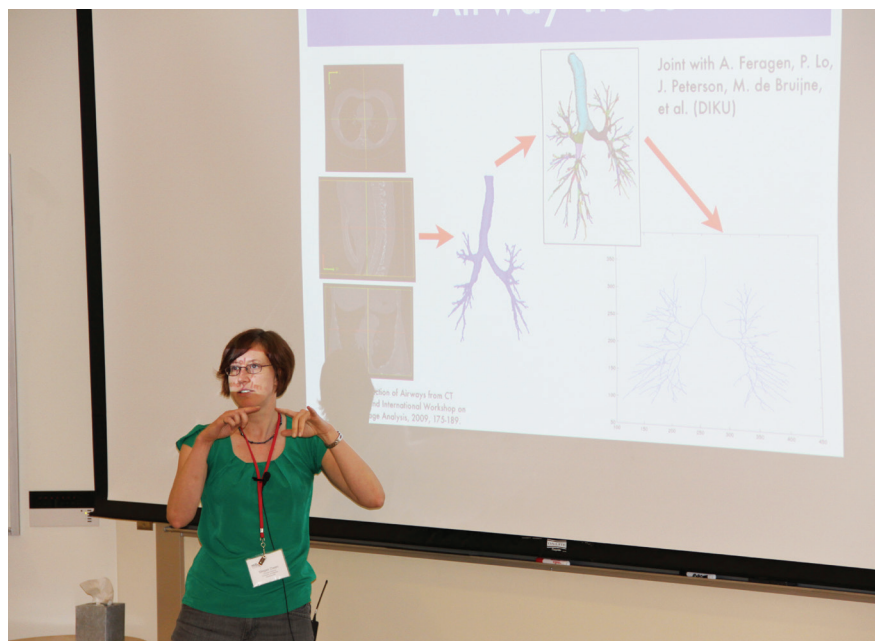
Megan Owen -University of Waterloo

As a practical question, the issue of interpretation of phylogenetic trees and the statistical significance of the level of differences between trees or groups of trees reconstructed by different methods or using different data, is of major importance. The issue with existing methods is that the distance between different trees is unlike conventional euclidian distances, which are used in other contexts. Dr. Owen shows that the subset of interior splits/partitions, which can exist together in the same tree, can be used to specify orthants used to define a unique shortest-path between any two trees, and thus a unique mid-point between any two trees. Furthermore, this distance can be calculated in polynomial time so that a mean tree and a variance can be calculated for groups of trees. These distances enable statistics to be efficiently computed, revealing the level of variance and bias associated with different methods.

Survey of stratified spaces

Robert MacPherson -Institute for Advanced Study

Dr. MacPherson provided an overview, directed towards a more general audience, to the theory of stratification of spaces, which describes such things as: the transition between a normal pendulum, and a weighted orbit; or, the distorted arcs gouged along surfaces by inelastic tools as manifolds or sets of manifolds. During this general background MacPherson describes the history of the study of manifolds and stratified spaces; with rousing discussion on probability measures of the corresponding spaces.



Megan Owen

The geometry and topology of projective shape space

John Kent -University of Leeds

Similarity shape space deals with configuration of points in finite dimensions that are invariant under similarity transformations, i.e., translation, rotations, and scaling. On the other hand projective shape analysis deals with configuration of collinear or coplanar points with properties invariant under the larger group of projective transformations. Even though the area of projective space is classical, new ideas are needed for its application in statistics. Perception of projective shape is crucial to human vision. An object with different image representations taken from multiple perspectives is naturally perceived as a single object in the brain. Projective geometry provides the theoretical framework to deduce 3D objects from multiple 2D images. Dr. Kent uses a spherical camera and ideas from the Procrustes approach to similarity shape analysis to give a standardized representation for projective shapes. The resulting geometry introduces a new metric on projective shapes given by this "Tyler" standardization. Singularities that appear in the metric definition require ideas from topology ideas for a clearer understanding. Classic projective shapes can be represented as an equivalence class of configurations. Finally, the details behind the standardization lead to a distinction between four variants of projective shape space depending on the type of



camera: oriented versus non-oriented, and directional vs. axial. Tyler standardization proves to be a powerful tool for quantitative comparison of different projective shapes.

Phylogenetic networks and the real moduli space of curves

Satyan Devadoss - Williams College

Phylogenetics is a widely researched topic in Mathematical Biology. This work is motivated by the configuration space of particles on spheres. Moduli space as n -punctured Riemann sphere with three points fixed on the spheres. Deligne-Mumford - Knudsen compactification allows the labeled points to collide. Dr. Devadoss studies the real moduli spaces and build the connection to phylogenetics tree space. Moduli spaces are smooth manifolds tiled by convex polytopes, and are an elegant topological space. Also, real moduli spaces appear in geometric group theory, representation theory, tropical geometry, cluster algebra, and as spaces of phylogenetic networks. Additionally there are pivotal biological applications of moduli spaces including its use in neighbor-joining and neighbor net algorithms. Moduli space resolves the singularities of Billera, Holmes, and Vogt-

mann (BHV) tree space by making it into a manifold. He then reviews the neighbor-net algorithm, which maps a dissimilarity matrix into a point in the moduli space. Dr. Devadoss then explained how to build the moduli space by compactification of configuration spaces. He gave examples of the Fulton-MacPherson compactification which allows multiple particle collision, and polydiagonal compactification which ranks the order of occurrence in addition to allowing multiple collisions. Moduli spaces are tiled by a convex polytope known as associahedra which then lead to a binary tree structure. There is a natural metric from the spaces of trees (BHV) into configuration spaces of points.

Wednesday

Object Oriented Data Analysis

Steve Marron - University of North Carolina

As a general framework, Object Oriented Data Analysis encompasses cases where statistics need to be done on complex objects (images, medical records, hierarchies, etc.); this framework provides a common point of refer-

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ence (a “language”) to discuss cases where the data is of greater dimension than the size of the sample. Dr. Marron connects this issue to independent developments in machine learning and non-parametric statistics. He begins with several examples from the subfield of functional data analysis, with a rousing discussion involving the audience, showing how principal component analysis can reveal, for example, historical events in mortality time series in Spain. Dr. Marron then talks about generalizing this kind of insight into strongly non-Euclidian spaces, such as phylogenetic trees or the manifolds used to analyze medical images. Referencing Dr. Owen’s talk from yesterday, unlike phylogenetic trees on the same group of leaves (organisms), the blood vessel trees characterizing medical images of various sorts do not share the same set of leaves (vessel termini.) The geodesic approach, combined with clever algorithmic flourishes, enables these diverse trees to be compared with practical computational complexity.

Sticky central limit theorems at singularities

Ezra Miller - Duke University

Dr. Miller raises a practical question: when samples are drawn from stratified spaces (for example from the space of trees), issues arise when attempts are made to apply the central limit theorem to the samples. For example, there are many different groups-of-sets-of-trees (or probability distributions of trees), with significant (not asymptotically small) differences among the sets/distributions of trees, which share the same mean - thus, the mean is “sticky,” not changing as you switch among these different sets. However, in other parts of the stratified space this property does not always hold. Problems of this kind can be categorized according to the level of stickiness (nonsticky - can be anywhere, sticky - is contained in a substratum, or partly sticky - meaning there is a boundry, as described in the case above). The upshot of this is that the classical assumptions of the law of large numbers/central limit theorem may not hold, and the mean of large samples will remain in some portion of the probability

space away from the mean of the underlying distribution.

This talk reports the results of a Statistical and Applied Mathematical Sciences Institute (SAMSI) program on the topic. The balance of the talk deals with particular cases. This talk featured frequent, lively and interesting questions throughout, as the participants reviewed the reported result.

Nonparametric Statistics on Manifolds – By Examples and applications

Rabbi Bhattacharya -University of Arizona

Dr. Bhattacharya reports joint work with his student, Vic Patrangenaru. The basic definition of a mean - the point in a space minimizing the expected squared-distance to a point in some distribution - is extended to deal non-parametrically with diverse spaces, manifolds and corresponding embeddings in lower-dimensional spaces. Using these methods, means can be calculated on spaces characterized by topologically-conserved landmarks (such as segmented medical images, satellite photos, and so forth.)

Bacterial trees in the human microbiome

Susan Holmes -Stanford University

Dr. Holmes works to combine phylogenetic and abundance data among human microbiomes (the bacteria living in each person) to characterize the diversity among



humans. She begins with a review of the relevant bacteriology, and the extensive relevance of this bacteriology to human disease. Numerous variables, associated with each individual, include: the abundance of each bacterial taxa in each location on a given person, the phylogenetic relationship among the bacteria which are observed, and the genes contained in those bacteria (which vary extensively). These data are highly heterogeneous, with abundances that vary across a huge scale, fuzzy distinctions between what does-and-does-not constitute the same strain of bacteria, and other issues which can have significant medical impact. Dr. Holmes has an integrated principle component method which incorporates all of this information; she reviews an application to the effect of antibiotics on the human microbiome. The end of the talk was an interesting discussion on open problems related to distances between and among trees, and on ways to decompose the principal component analysis into individually significant differences (e.g., specific species of bacteria which change in abundance in response to treatment.)

Thursday

On omitting and hitting properties for means on circles and shape spaces

Stephen Huckemann - Georgia Augusta University Goettingen

The classical central limit theorem states that suitably translated and root n rescaled independent sample means tend to a multivariate Gaussian. Under certain restrictive conditions, it has been shown by Bhattacharya and Patrangenaru in 2005 that the analog holds true on manifolds. One condition, namely uniqueness has been pushed to “data contained in a geodesic half ball” by Afshari in 2011, which in particular encompasses “omitting a neighborhood of the cut locus” if non-void. Determining asymptotics when the cut locus is not omitted proves to be challenging. For circles Dr. Huckemann and his collaborator Dr. Thomas Hotz develop an exhaustive treatment of uniqueness and, in view of asymptotics, of the role of mass around the antipodal point.

Geometry and statistics in the Eigen-structure of symmetric (Positive semi-definite) matrices

Armin Schwartzman - Harvard School of Public Health

As symmetric positive semi-definite (PSD) matrices appear as data objects in the statistical analysis of Diffu-

sion Tensor Imaging data, and there is interest in making inferences about the eigenvalues and eigenvectors of these objects. Dr. Schwartzman present a stratification of the set of symmetric PSD matrices of arbitrary dimension according to their eigenvalues, as well as maximum likelihood estimators (MLEs) and log-likelihood ratio (LLR) tests for the eigenvalues and eigenvectors of the mean matrix in a symmetric-matrix Gaussian model. The parameter sets involved are subsets of Euclidean space that are either affine subspaces, polyhedral convex cones, or orthogonally invariant embedded submanifolds. The conclusion is that the stratum where the true mean matrix lies determines the asymptotic behavior of the MLEs and LLRs.

Manifold-valued Tuning parameters in regularized estimation of multivariate means

Rudolf Beran - University of California, Davis

A multivariate k -way layout consists of observations with error on an array of vector-valued means, each of which is an unknown function of k real-valued covariates. Any decomposition of these vector means into a sum of orthogonal projections induces least squares submodel fits that serve as candidate estimators of the mean vectors. Dr. Beran described penalized least squares estimators of the multivariate means in which the penalty terms are weighted through manifold-valued tuning parameters. Data-based selection of the tuning parameters yields estimators that dominate asymptotically those that arise from submodel fitting. And the speaker discusses the special case of a complete balanced multivariate k -way layout, when the proposed regularized estimators are linked to multiple Efron-Morris affine shrinkage.

The geometry and statistics of geometric trees

Aasa Feragen - University of Copenhagen

Anatomical tree-structures such as airway trees from lungs, blood vessels or dendrite trees in neurons, carry information about the organ that they are part of. Anatomical trees can be modeled as geometric trees, which are combinatorial trees whose edges are endowed with edge attributes describing their geometry. Dr. Feragen discusses different ways of building spaces of such geometric trees, all with the goal of obtaining a geodesic space of trees where statistical parameters can be computed with the help of geodesics. For geometric trees of any size, one can define a geodesic space of trees, but

Statistics, Geometry, and Combinatorics on Stratified Spaces Arising from Biological Problems

many statistical tools are not readily available for geodesic computations. By adding restrictions on size, admissible topologies, branch order and/or branch labeling, the speaker proposed that people can regularize the space in order to obtain spaces which have nicer properties in terms of computational complexity and statistical applications. Dr. Feragen also discusses the effect of these assumptions on the solvability of statistical problems and presents some recent results from experiments on airway trees from lung CT scans.

*The multiresolution Dantzig selector:
From ion channel recordings to biomolecular microscopy*

Axel Munk -University of Goettingen

Dr. Munk introduced the multiscale Dantzig selector in the particular context of signal detection and imaging. This method allows combining variational regularization methods with statistical multiscale techniques in a statistical sound manner. He addressed computational issues as well as asymptotic stochastic process theory of the multiscale statistics, and he also discusses in detail the modeling of ion channel recordings and reconstruction in nanoscale biophotonic cell microscopy.

Friday

Mean location, the two sample problem

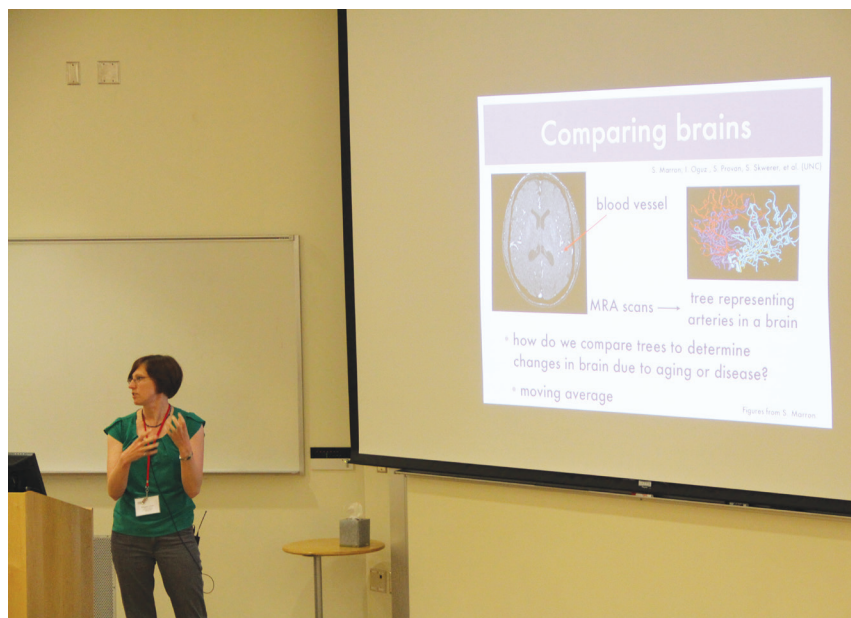
Harrie Hendriks -University Nijmegen

Dr. Hendriks discussed the estimation of a parameter of a probability distribution, where the parameter lies in a differentiable manifold, more specifically in a submanifold of Euclidean space. The parameter could be a Frechet mean of a probability distribution on the submanifold itself, Frechet mean with respect to the Euclidean distance. An account of the two-sample problem was given.

Topological Analysis of Variance and the Maxillary complex

Giseon Heo -University of Alberta

It is common to reduce the dimensionality of data before applying classical multivariate analysis techniques



in statistics. Persistent homology, a recent development in computational topology, has shown to be useful for analyzing high dimensional (non-linear) data. Dr. Heo connected computational topology with the traditional analysis of variance and demonstrated this synergy on a three-dimensional orthodontic landmark data set derived from the maxillary complex. He showed that combining appropriate techniques of both persistent homology and analysis of variance results in a better understanding of the data's non-linear features over and above what could have been achieved by classical means.

Riemannian barycenters: from harmonic maps and statistical shape to the classical central limit theorem

Wilfrid Kendall -University of Warwick

The subject of Riemannian barycentres has a strikingly long history, stretching back to work of Frechet and Cartan. Dr. Kendall first reviewed the fundamental ideas and discussed the work of various probabilists and statisticians on applications of the concept to probabilistic approaches to harmonic map theory and statistical shape theory. Then he presented some recent joint work with Huiling Le concerning central limit theory for empirical barycentres, which led to a new perspective on the classical Lindeberg-Feller central limit theorem.

Undergraduate Program (May 29 - August 17, 2012)



In 2012, MBI markedly extended our summer research program for undergraduates and began a new national Institute Partner's Joint Research Experience for Undergraduates (REU). 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 (May 29 - June 8, 2012); an eight-week individualized research experience as part of a research team at one of the seven participating host institutions; and a week-long Capstone Conference.

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. Hal Smith continued the dynamical systems theme with a tutorial on their use in species competition and cooperation. Giovana Guidoboni provided an introduction to fluid dynamics and the partial differential equations used in tissue and blood modeling. Dan Janies showed the students his research in computational biology and the evolution of diseases and Dennis Pearl continued the unit with a discussion of estimating evolutionary histories using the tools of statistical phylogenetics. Neuroscience was the next unit with Bard Ermentrout and Janet Best providing tutorials on computational and mathematical neuroscience respectively. Finally, the tutorials were completed with Krešimir Josić giving an overview of probability modeling in biology. 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, XPPAUT, and various web applications thanks to the guidance of MBI postdocs Rebecca Tien and Sam Handelman and Ohio State graduate student Jung Eun Kim.



During the two-week program, the students also toured labs that use quantitative methods in the biological and medical sciences. This included a tour of the Illumina Next Generation Sequencing Lab where Pearly Yan guided the students through the computationally intensive work of the lab. 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. Bianca Bernal provided the group with a hiking tour through the living laboratory of the Olentangy River Wetland Research Park and their projects in ecological engineering. 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. In the final tour, the students paid a visit to Libby Marschall's aquatic ecology laboratory where her team of graduate students showed off their work in studies of fish populations in Lake Erie.

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. These included projects at Arizona State University supervised by Fabio Milner and Jay Taylor; at Indiana University-Purdue University Indianapolis supervised by Giovanna Guidoboni and Leonid Rubchinsky; at University of Minnesota supervised by Hans Othmer and Duane Nykamp; at Ohio State University supervised by Laura Kubatko and Dennis Pearl; at University of Pittsburgh supervised by Brent

Doiron, Bard Ermentrout, and Jon Rubin; at the Virginia Biomathematics Institute at Virginia Tech supervised by Reinhard Laubenbacher; and at University of Houston supervised by Kresimir Josic and Will Ott.

The Summer Program ended with a weeklong Capstone Conference celebrating all of the nationwide efforts of undergraduate researchers in the mathematical biosciences – not just those of the 15 MBI sponsored students. This student-centered conference featured a graduate studies recruitment fair for Institute Partner Schools (11 programs participated); panel discussions on job 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 27 half-hour oral presentations and 33 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 seven 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.

Graduate Workshop on Stochastics Applied to Biological Systems (June 18-29, 2012)

Organizers: Linda Allen (Texas Tech), Laura Kubatko (OSU), Suzanne Lenhart (UT Knoxville), Libby Marschall (OSU), and Lea Popovic (Concordia U)

A total of 46 graduate students from mathematics and biology participated in the workshop. Topics included Markov chains, birth-death processes, branching processes, stochastic differential equations, stochastic dynamics, diffusion, stochastic agent-based models, stochastic networks, stochastic epidemiology, and phylogenetics.

The workshop began with a day of lectures and activities designed and presented by Lou Gross (NIMBioS) to introduce students to the main concepts necessary for working with stochastics in biology. The rest of the program featured four pairs of researchers from the mathematical and biological sciences who each spent two days introducing students to theory and applications through lecture and hands-on analysis and simulation activities. Each lecturer also provided a project for a small group of students (4-6 students) to work on over the course of the 12-day program. Nine postdoctoral and senior predoctoral researchers (6 MBI, 1 NIMBioS, 1 UC-Davis, 1 U Idaho) assisted the lecturers and helped guide the small-group projects. On the final day of the workshop, we held a mini-symposium during which students presented the results of their small-group projects to the entire group.



The lecturers and their topics were:

- Lou Gross (NIMBioS), *An introduction to thinking like a probabilist about biology*
- Linda Allen (Texas Tech), *An introduction to stochastic epidemic models*
- Edward Allen (Texas Tech), *A Practical introduction to stochastic differential equations in mathematical biology*
- David Anderson (U Wisconsin), *Markov chain models used in biology: models, approximations, and simulation*
- Scott McKinley (U Florida), *Anomalous diffusion in biological fluids*
- Steve Krone (U Idaho), *Individual-based stochastic spatial models*
- Nicolas Lanchier (Arizona State), *Flux and fixation for the voter model and the Axelrod model*
- Dennis Pearl (OSU), *Markov models of molecular evolution, Bayesian phylogenetics, and the MCMC approach*
- Sebastian Schreiber (UC-Davis), *Persistence, coexistence and spatial spread in a fluctuating environment*

Colloquium

ANTHONY R. IVES -Department of Zoology, University of Wisconsin-Madison

Alternative states in long-term ecological time series (September 26, 2011)

GUIDO MARCUCCI -Internal Medicine, Division of Hematology & Oncology, OSU

Gene-microRNA networks in Acute Myeloid Leukemia: biology, prognostic and therapeutic implications (October 3, 2011)

DALIN TANG -Mathematical Sciences, Worcester Polytechnic Institute

Computational Human Ventricle Models for Surgical Optimization Based on Patient-Specific Magnetic Resonance Imaging (October 17, 2011)

STEVE COX -Computational & Applied Mathematics, Rice University

Toward a minimal model of a large spiking cell (October 31, 2011)

RUSS HILLE -Biochemistry, University of California, Riverside

Mathematical Models for Enzyme Reactivity: A Case Study in Xanthine Oxidase (November 7, 2011)

LEONID BERLYAND -Mathematics, Penn State University

Kinetic models of swimming bacteria in semi-dilute limit (November 21, 2011)

ANASTASIOS MATZAVINOS -Mathematics, Iowa State University

Random walk distances in data clustering and applications (November 28, 2011)

BRENT LINDQUIST -Applied Mathematics & Statistics, Stony Brook University

Data-Based Analysis of Winner-Loser Models of Hierarchy Formation among Animals (January 9, 2012)

MARK BERLINER -Statistics, The Ohio State University

Statistical Approaches to Combining Models and Observations (January 23, 2012)

LINDA ALLEN -Mathematics & Statistics, Texas Tech University

Extinction Thresholds in Deterministic and Stochastic Models for Epidemics and Viral Dynamics (February 13, 2012)

SARAH J. WHEELAN -Johns Hopkins Medical Institute

The “top ten” are just the tail: A correlation method to uncover the rest of the elephant in high throughput biology data (February 27, 2012)

XIHONG LIN -Biostatistics, Harvard University

Design and Analysis of Whole Exome (Genome) Sequencing Association Studies (March 5, 2012)

PAUL BRESSLOFF -Mathematics, University of Utah

Traveling waves in a neural field model of binocular rivalry (April 2, 2012)

BRIAN SMITH -Entomology, Arizona State University

Plasticity in early sensory coding: It's role in solving the generalization problem for complex, variable natural odors (April 9, 2012)

GREG WRAY -Biology, Duke University

Evolutionary origins of human transcriptomes (April 23, 2012)

Postdoc Seminars

FRANZISKA HINKELMANN

Algebraic theory for discrete models in systems biology (September 8, 2011)

ARJUN BERI

Estimation of stochastic models under indirect observability (September 22, 2011)

HYE-WON KANG

A method for choosing the computational cell in stochastic reaction-diffusion systems (September 29, 2011)

DUAN CHEN

Quantum dynamics in continuum model for proton transport in membrane channels (October 6, 2011)

BLERTA SHTYLLA

Modeling of a chromosomal "One-Shot" polymer motor (October 20, 2011)

HARSH JAIN

A non-autonomous delay differential equation model of cancer chemotherapy (November 3, 2011)

MARISA EISENBERG

Identifiability and estimation of multiple transmission pathways in waterborne disease (November 10, 2011)

SHU DAI

Cardiac restitution and alternans dynamics (December 1, 2011)

JUAN GUTIERREZ

Modeling multi-sexual populations: Methods and applications (December 8, 2011)

PAUL HURTADO

Immune-Pathogen Dynamics & Modelling Simple Multispecies Interactions (January 19, 2012)

JON LO

Feedback Regulation and Spatial Control of Multistage Cell Lineages (January 26, 2012)

CASEY DIEKMAN

Using noisy inputs to prevent infant apnea (February 2, 2012)

RACHEL LEANDER

A Mathematical Model of CR3/TLR2 Crosstalk in the Context of Francisella tularensis Infection (February 16, 2012)

REBECCA TIEN

Population growth and vertical distribution of light-limited phytoplankton under non-homogenous grazing pressure (March 1, 2012)

SAM HANDELMAN

PhyloPTE/Peacefield - Phylogenetic Reconstruction used to improve the power of genome wide association studies (GWAS) (March 15, 2012)

SUZANNE ROBERTSON

Modeling the spread of waterborne disease: the role of heterogeneity in dual transmission pathways (March 29, 2012)

Visitor Seminars

ANASTASIOS MATZAVINOS -Iowa State University

A stochastic analysis of the motion of DNA nanomechanical bipeds (September 6, 2011)

VLASTIMIL KRIVAN -Biology center, Ceske Budejovice, Czech Republic

Population and behavioral models in ecology: Hanging together or hanging separately? (September 19, 2011)

DEBASHISH CHOWDHURY -Physics, Indian Institute of Technology, Kanpur

Stochastic kinetics of molecular motors: mathematical models of kinesin and ribosome (September 20, 2011)

THOMAS KURTZ -University of Wisconsin - Madison

Genealogical constructions of measure-valued models in population genetics (September 27, 2011)

GREG REMPALA -Medical College of Georgia

Biochemical rates inference from trajectory data (October 4, 2011)

JOAQUIN RIVERA-Cruz -Colgate University

Persistence of competitors in deterministic and variable patchy environments (October 18, 2011)

DONG LI -Mathematics, University of Iowa

The Euler-Poisson system in plasma physics (November 1, 2011)

PETER THOMAS -Case Western Reserve University

Phase Resetting in an Asymptotically Phaseless System: On the Phase Response of Limit Cycles Verging on a Heteroclinic Orbit (November 8, 2011)

ZHI AN WANG -The Hong Kong Polytechnic University

Anisotropic diffusion chemotaxis models derived from stochastic equations (November 22, 2011)

ELISSA SCHWARTZ -Washington State University

Predicting Vaccine Strategies for Viral Infections (November 29, 2011)

PETE KRAMER -Mathematical Sciences, RPI

Collective Stochastic Dynamics of Microbiological Systems (January 17, 2012)

ED ALLEN -Math & Stats, Texas Tech University

Some Work On Stochastic Differential Equation Models In Mathematical Biology (January 24, 2012)

RONGSONG LIU -University of Wyoming

Spatiotemporal Mutualistic Model of Mistletoes and Birds (January 31, 2012)

JONATHAN MATTINGLY -Mathematics, Duke University

Propagating Lyapunov Functions to Prove Noise-Induced Stabilization (February 14, 2012)

SCOTT MCKINLEY -Mathematics, University of Florida

Diffusion in Biological Media (March 27, 2012)

JOHN MCSWEENEY -SAMSI

Stochastic Bistability in Chemical Reaction Systems with Resampling (April 10, 2012)

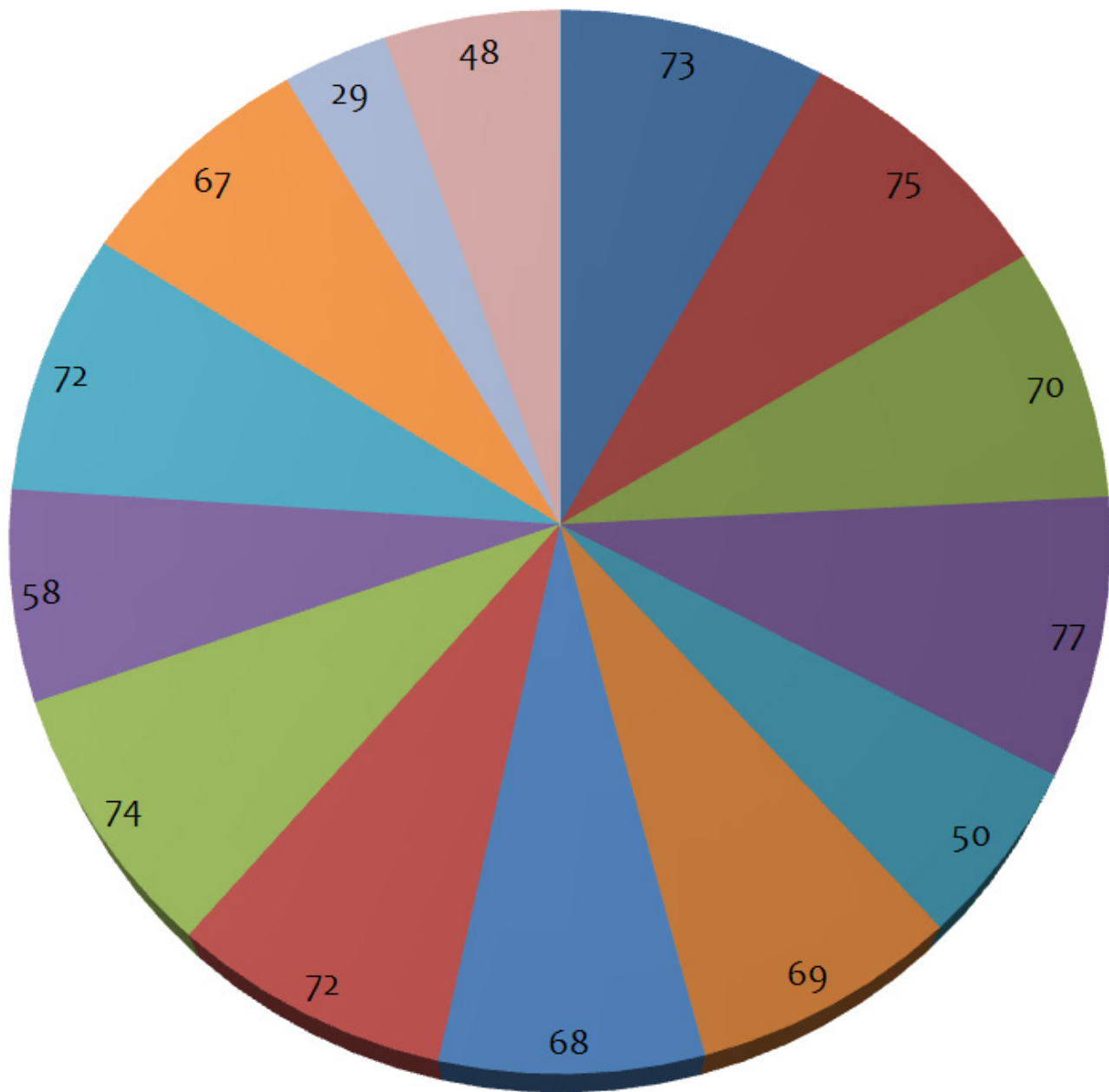
REINHARD LAUBENBACHER -Bioinformatics Institute, Virginia Tech

Trends in algebraic methods for systems biology (May 18, 2012)

BRANDY STIGLER -Southern Methodist University

Comparing knowledge-driven and data-driven models of tissue development in *C. elegans* (May 16, 2012)

The chart below shows the total number of participants for each MBI event during the 2011-2012 emphasis year. The total number of participants this year was 902.

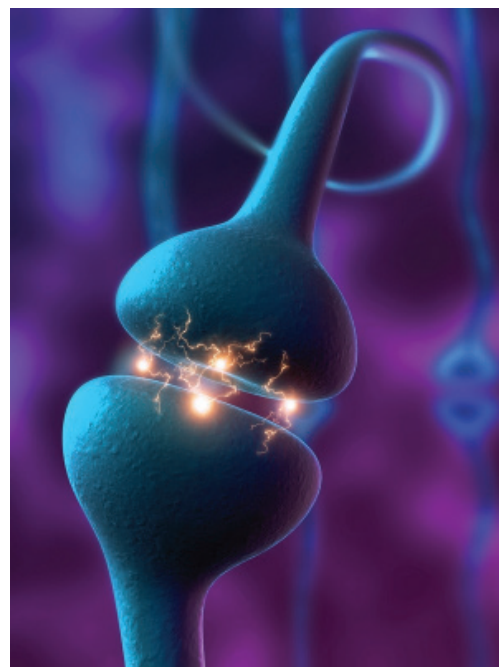


- WYRMB
- Workshop 1: New Questions in Probability Theory Arising from Biology
- CTW: Spatio-Temporal Dynamics in Disease Ecology and Epidemiology
- Workshop 2: Stochastic Processes in Cell and Population Biology
- CTW: Free Boundary Problems in Biology
- Workshop 3: Robustness in Biological Systems
- CTW: Recent Advances in Statistical Inference for Mathematical Biology
- Workshop 4: Evolution and Spread of Disease
- Workshop 5: Spatial Models of Micro and Macro Systems
- CTW: Tissue Engineering and Regenerative Medicine
- Workshop 6: Algebraic Methods in Evolutionary and Systems Biology
- CTW: Statistics, Geometry, and Combinatorics on Stratified Spaces Arising from Biological Problems
- Summer Undergraduate Program
- Summer Graduate Program

Mathematical Neuroscience July 2012 - June 2013

Organizers: Carmen Canavier (LSU), John Rinzel (NYU), Steve Schiff (Penn State), Eric Shea-Brown (Washington), Murray Sherman (Chicago)

Mathematics describes key dynamical mechanisms for patterns of neural activity and quantifies levels of information in these patterns. At the same time, new mathematics, that often bridges information theory, dynamical systems, and statistical mechanics, has been inspired by the complexity of the underlying networks and the computations they perform. Over the past decade, mathematics has entered different subfields of neuroscience, and has suggested unexpected parallels among others.



July 16-20, 2012	MBI BioSciences Problem-Solving Workshop (PSW@MBI)
August 27-31, 2012	Workshop for Young Researchers in Mathematical Biology
September 19-21, 2012	Mathematical Biology: Looking at the Future
October 1-5, 2012	Workshop 1: Mathematical Challenges in Neural Network
October 15-18, 2012	Mathematical and Computational Challenges in Cilia- and Flagella-Induced Fluid Dynamics
November 13-16, 2012	Statistics of Time Warpings and Phase Variations
December 10-14, 2012	Workshop 2: Cognitive Neuroscience
February 4-8, 2013	Workshop 3: Disease
February 18-22, 2013	Mathematical Advances in Biomolecular/Biomedical Imaging and Visualization
March 18-22, 2013	Workshop 4: Rhythms and Oscillations
April 8-12, 2013	Workshop 5: Cellular and Subcellular
May 6-10, 2013	Workshop 6: Sensory Systems and Coding
June 24-28, 2013	Keyfitz Symposium on Mathematical Demography

Ecosystem Dynamics and Management

Fall 2013

Organizers: Jordi Bascompte (CSIC), Chris Cosner (Miami), Alan Hastings (UC Davis), Marc Mangel (UC Santa Cruz), Jim Sanchirico (UC Davis), Mary Lou Zeeman (Bowdoin)

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 will highlight both the biological and mathematical issues involved. We envision three related workshops. 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.

July 29 - August 2, 2013	Teaching Discrete Algebraic Mathematical Biology to Undergraduates
August 26-29, 2013	Workshop for Young Researchers in Mathematical Biology
September 16-20, 2013	Workshop 1: Sustainability and Complex Systems
October 7-11, 2013	Workshop 2: Rapid Evolution and Sustainability
October 28-November 1, 2013	Mathematics Guiding Bioartificial Heart Valve Design
November 4-8, 2013	Workshop 3: Sustainable Management of Living Natural Resources



B. AGUDA, Y. KIM, H. KIM, A. FRIEDMAN, AND H. FINE

Qualitative network modeling of the MYC-p53 control system of cell proliferation and differentiation
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