2010-2011



Evolution, Synchronization, and Environmental Interactions: Insights from Plants and Insects

mbi
Mathematical Biosciences Institute

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

Contents


Fibonacci sunflower

Safari ant soldiers by Mehmet Karatay

Message from the Director

MBI just completed its ninth year of programming. *Plants and Insects* (as we call it internally) was a great success and I would like to thank the emphasis year organizers (Vince Gutschick, Danny Forger, Mark Lewis, Scott Nuismer, David Rand, and David Sumpter) for their guidance in assembling the program. In this message I want to highlight some of the events that occurred at MBI during the past year.

During 2010-11, MBI held its first competition for *Current Topic Workshops* (the second CTW competition is now under way), experimented with a new workshop format (a *Bootcamp on Cancer Modeling* aimed at bioscientists), and had the honor of hosting the sixth *Blackwell-Tapia Conference*. I want to take this opportunity to congratulate Trachette Jackson who received the *2010 Blackwell-Tapia Prize* "in recognition of her outstanding contributions to the modeling of solid tumor growth and for serving as a role model for diversity in the mathematical sciences."

By contrast to the onetime meetings, MBI has a program that has become a fixed point in our schedule: the *Workshop for Young Researchers in Mathematical Biology*. WYRMB is a networking conference, organized by the MBI post-docs, that is aimed at researchers from advanced graduate students to untenured faculty. As expected, the seventh meeting of WYRMB was a great success.

MBI is a community resource and we are constantly looking for additional ways to improve this resource. We mention five that occurred in 2010-11.

All MBI talks are now live video streamed. We expect more people to take advantage of this way of viewing MBI talks as this resource is better known.

MBI sponsors one course per semester aimed at MBI postdoctoral fellows. The course lectures are also live video streamed.

The MBI *Visiting Lecturer Program* began in 2010. This program sponsors undergraduate level lectures by prominent mathematical biologists at institutions with strong minority enrollments. Information about the VLP program can be found at http://mbi.osu.edu/about/vlprogram.html

The first competition for MBI's new *Early Career Awards* program occurred in 2010. This program enables long-term visits to MBI by untenured faculty in tenure-track positions whose research coordinates with MBI's emphasis year programs.

2010-11 also witnessed a continued expansion in the MBI Institute Partner program. MBI now has 42 IPs. We very much appreciate the support that MBI receives from these institutions, ranging from help in creating and choosing MBI programs to the mentoring of MBI postdoctoral fellows.

Since MBI began its programming in 2002, forty-two postdoctoral fellows have completed their training. In addition, 16 post-docs were in residence in 2010-11. The program remains strong and MBI is currently advertising for new post-docs to begin in September 2012.

MBI views the interaction between the mathematical sciences and the life sciences as a two-way interaction, which we summarize by the phrases *Math to Bio* and *Bio to Math*. Traditionally, MBI workshops have stressed *Math to Bio* by showcasing the many ways in which the mathematical sciences can prove useful in the life sciences (from the creation, computation, and analysis of models to the education of bioscientists in quantitative techniques). MBI's five-year NSF renewal grant began in September 2010. Our proposal promised to increase the number of MBI programs and, in particular, to increase the number of *bio to math* programs; and we are doing just that.

Our renewal grant also allows MBI to help fund more long-term visitors (for stays of a month or more in support of MBI emphasis year programs) and to supplement our summer education offerings.

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.

Current Institute Partners

- Arizona State University
- Batelle
- 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
- Legacy Good Samaritan Hospital
- Michigan State University
- New Jersey Institute of Technology
- Ohio State University
- Ohio University
- Penn State University
- Princeton University
- Texas Tech University
- University of California, Irvine
- University of Cincinnati
- University of Exeter
- University of Georgia
- University of Houston
- University of Iowa
- University of KwaZulu-Natal
- University of Maryland, Baltimore County
- University of Miami
- University of Michigan
- University of Minnesota
- Universidad Nacional Autónoma de México
- University 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
- Vanderbilt University
- Virginia Tech

OUR MISSION IS...

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

Postdoctoral Fellow 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

EARLY CAREER AWARD PROGRAM

Early Career Awards enable recipients to be in residence for stays of at least three months during an Emphasis Year Program at the Mathematical Biosciences Institute. The 2011-12 Program is on Stochastics in Biological Systems (see http://mbi.osu.edu/2010/scientific2011.html). Awardees will engage in an integrated program of tutorials and workshops tied to the scientific theme and are expected to interact with local and visiting researchers.

Early Career Awards are aimed at non-tenured scientists who currently have continuing employment and who hold a doctorate in any of the mathematical, statistical and computational sciences, or in any of the biological, medical and related sciences.

PROGRAM IDEAS

MBI programs are aimed at bringing mathematical scientists and bioscientists together to discuss ways in which the mathematical sciences are being used to solve significant problems in the bio and biomedical sciences or how problems from the biosciences are opening new areas of research for mathematicians, statisticians, and computational scientists.

MBI encourages members from the mathematical sciences or the biosciences community to propose ideas for MBI programs.

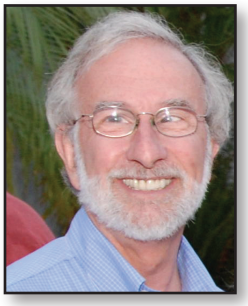
MBI programs fall roughly into three categories:

- Semester or yearlong emphasis programs (consisting of a number of related workshops and supported by MBI long-term visitors).
- Current Topic Workshops (typically stand alone meetings of up to one week).
- Education programs.

For details on how to submit an idea for an MBI program, visit:

http://www.mbi.osu.edu/suggestions.html

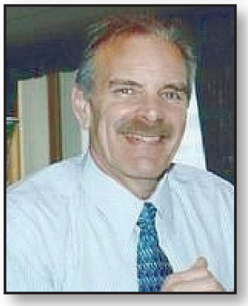
Directors



Professor 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.



Professor 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.

Four **Associate Directors** provide scientific advice and support to the director. All Associate Directors are involved in the mentoring program for postdoctoral fellows. Each Associate Director oversees at least one aspect of MBI.

Professor Helen Chamberlin

Associate Director

Works with the director of diversity issues.

Professor Yuan Lou

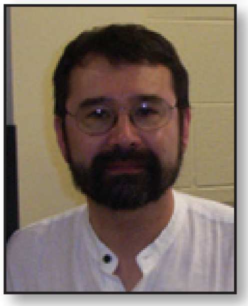
Associate Director

Oversees the postdoctoral fellow program and edits the MBI Newsletter.

Professor Dennis Pearl

Associate Director

Responsible for the education programs, as well as the evaluation process.



Professor Andrej Rotter

Associate Director

Provides leadership for relations between MBI and the Ohio State Medical Center.

Professor Tony Nance

Assistant Director

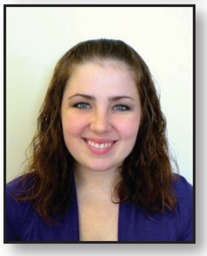
Duties include oversight of the day-to-day operation of the MBI offices and supervision of the institute staff.

Staff

Nikki Betts

Financial and HR Manager

Manages all human resources and financial activity in the MBI, including visa, travel, and reimbursement related activities. She also helps with program and reporting activities.



Rebecca Boroff

Program Assistant

Provides point of contact for all MBI visitors. Assists Matt Thompson in processing travel reimbursements and event coordination. Also provides IT support such as resolving tickets and videotaping events taking place at MBI.

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

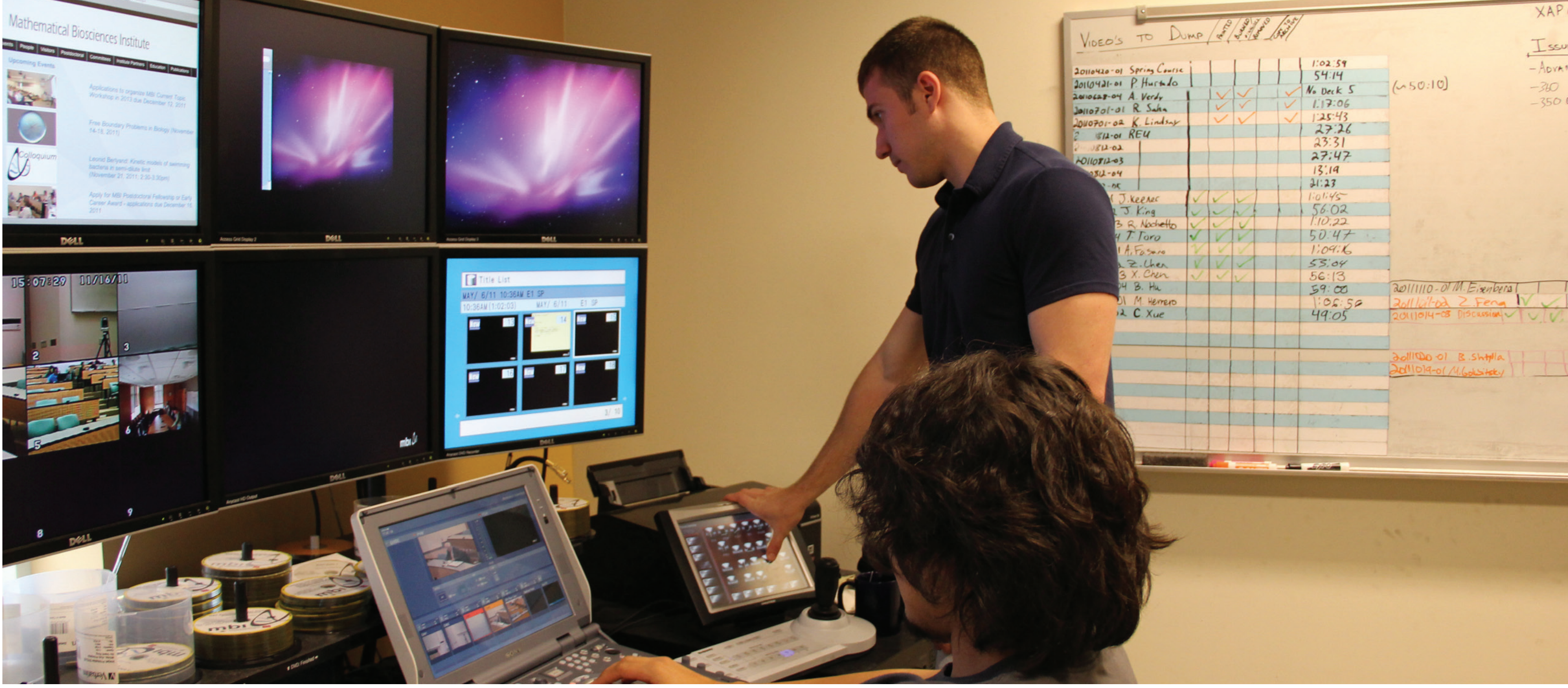
Program Assistant

Provides point of contact for all MBI visitors. Assists Matt Thompson in processing travel reimbursements and event coordination. Also provides IT support such as resolving tickets and videotaping events taking place at MBI.

Rebecca Martin

Office 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

Assists in fiscal processing, registration, reimbursements, human resources, and event coordination; responsible for information given to all visitors.

Caitlin Naber
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.

Postdoctoral Fellows

Julia Chifman

(Mathematics, University of Kentucky) Julia's research primarily focuses on phylogenetic invariants and their performance under the coalescent process (joint work with Laura Kubatko, OSU). Although much progress on phylogenetic invariants has previously been made for a single gene, it is well-known that gene trees are not topologically equivalent with the species tree. By deriving phylogenetic invariants within the coalescent framework, her work extends their utility to the case of multi-gene data for which the goal is inference of the species-level phylogeny. She is also interested in the analysis of the mammalian iron metabolism using algebraic tools (joint work with Reinhard Laubenbacher, Virginia Tech).

Shu Dai

(Mathematics, Duke University) 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, University of Michigan) Casey's research interests are in mathematical neuroscience and biological rhythms. His dissertation was on modeling the electrophysiology of the mammalian circadian clock and statistical inference of functional connectivity from multi-neuronal spike trains. While at MBI, Casey plans to use simulation and dynamical systems analysis tools to study the neuronal bursting underlying breathing, the role of mitochondrial excitability in stroke, taste processing, and the circadian clock in the retina.

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 my current projects and collaborations include: algebraic and numerical methods for identifiability, uncertainty quantification, and parameter estimation; cholera disease transmission dynamics & spatial heterogeneity; feedback regulation and the human hypothalamic-pituitary-thyroid axis; cellular invasion & migration in cancer; 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.

Richard Gejji

(Mathematics, University of Notre Dame) Richard is using mathematics to understand how micro-organisms aggregate and swarm under volume exclusion conditions. By using computer simulations and continuous limit partial differential equations with nonlinear diffusion, it is possible predict the macroscopic behavior of the microbes. These predictions will provide new insights into when they can aggregate together and form structures capable of defending against traditional anti-biotic treatments. He is also studying problems in ecology concerning when speciation events may occur and when new species can coexist as the result of different movement strategies.

Juan Gutierrez

(Mathematics, Florida State University) 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 in 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 University, New York) 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.

Harsh Jain

(Applied Mathematics, University of 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.

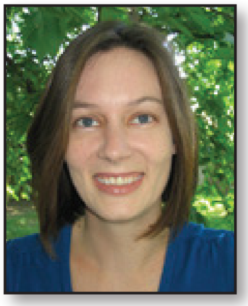
Rachel Leander

(Mathematics, University of 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 Porphyoromonas 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.

Postdoctoral Fellows

Annie Lindgren

(Division of Biological Infrastructure, NSF) Large-scale shifts in habitat during evolution require lineages to respond to new selective pressures, often resulting in a cavalcade of novel morphologies. In cases where unrelated lineages occupy similar or sympatric habitats, similar characteristics often arise independently, resulting in convergence. Annie's research examines convergent evolution in the enigmatic marine invertebrate class Cephalopoda. Cephalopods have transitioned from benthic to pelagic habitats multiple times, resulting in a cavalcade of novel morphologies. To uncover the molecular mechanisms influencing convergence, she utilizes next-generation techniques to analyze gene expression patterns in the cephalopod cornea, a structure that has arisen independently in squids and octopuses.



Suzanne Robertson

(Applied Mathematics, University of Arizona) Suzanne's research interests are in mathematical ecology, epidemiology, and evolutionary biology. Her current projects include the following: using periodically forced differential equations to identify the main seasonal drivers of cholera and account for the different outbreak patterns between geographical regions; investigating the role of the risk of infectious disease on optimal habitat selection; modeling spatial distributions resulting from predator-prey interactions in vertical water columns in hypoxic lakes; studying the effect of size-dependent interactions within a food web on alternate stable states.

Deena Schmidt

(Applied Mathematics, Cornell University) Deena develops and analyzes mathematical models to understand the roles of stochasticity, structure, and evolution in shaping the dynamics of biological systems at different scales. Her current work focuses on modeling the neuronal network structure and stochastic dynamics involved in the regulation of sleep and wake behavior. She explores these issues using random graph theory, specifically looking at stochastic processes occurring on random graphs, and also by investigating the accuracy of predictions made by deterministic approximations of stochastic processes on networks.

Dan Siegal-Gaskins

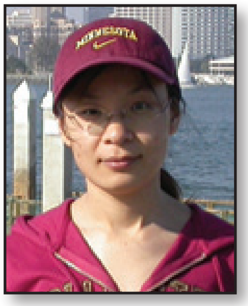
(Physics, University of Chicago) Dan is currently using a combined experimental and mathematical approach to understand the mechanisms that lead to cell fate determination. In particular, he is investigating whether a simple gene regulatory network underlying the development of unicellular leaf hairs (trichomes) in the model system Arabidopsis thaliana has the capacity for bistability, and if that bistability can explain the characteristic trichome pattern. He is also studying the role of global leaf properties in selecting the location for the very first trichome cell differentiation event.

Rebecca Tien

(Ecology and Evolutionary Biology, Cornell University) 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.

Yunjiao Wang

(Mathematics, University of Houston) Yunjiao works in the fields of nonlinear dynamical systems and system biology. Her recent research on nonlinear dynamical systems focuses on studying dynamics of networks, especially on studying general theory of coupled cell systems, functions of motifs, coupled oscillators and transtivity of oscillations. Her current research on system biology focuses on studying heterochronic signaling pathways in C. elegans and nuclear factor \kappaB signaling pathways, especially its interaction with other signaling pathways in the cell and between cells.



Chuan Xue

(Applied Mathematics, University of Minnesota Twin Cities) Chuan Xue's research involves multi-scale modeling in bacterial pattern formation and wound healing. She has developed a hybrid cell-based model which incorporates intracellular signal transduction, cell movement and extracellular signal dynamics. The model yields biologically-based explanations to radial and spiral stream formation in P. mirabilis colonies. To reduce the computational cost due to large number of cells, she lifted the cell-based model to a continuum model by deriving macroscopic chemotaxis equations of cell density using perturbation techniques and moment closure methods. She is also working on mathematical models for ischemic wound healing. The goal is to understand how the supply of oxygen affects the wound healing process and how hyperbaric treatment helps with chronic wound closure in patients with circulation diseases.

Kun Zhao

(Mathematics, Georgia Institute Of Technology) Kun's research interests are in the area of analysis and applications of nonlinear partial differential equations (PDEs) in various branches of science and engineering. In his Ph.D. thesis, he studied qualitative behavior of solutions to initial-boundary value problems for several systems of nonlinear evolutionary partial differential equations arising from fluid dynamics and civil engineering. At MBI he is currently working on several systems of PDEs arising from mathematical biology, namely, the Keller-Siegel type chemotaxis models and the Cahn-Hilliard-Hele-Shaw equations.

Committees

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.
Current Members

- Rita R. Colwell, Distinguished University Professor, Center for Bioinformatics and Computational Biology, University of Maryland, College Park (12/31/13)
- John Guckenheimer, Mathematics, Cornell University (12/31/11)
- Kirk E. Jordan, Emerging Solutions Executive, Computational Science, IBM T.J. Watson Research Center (12/31/11)
- Mark Lewis, Mathematical Sciences, University of Alberta, Canada (12/31/11)
- Robert M. Miura (Chair), Mathematical Sciences, New Jersey Institute of Technology, Newark, New Jersey
- Blake Thompson, Ph.D., Vice President, Institutional Affairs, Battelle Columbus, OH (12/31/12)
- Michael Waterman, Biological Sciences, Mathematics, Computer Science, University of Southern California (12/31/12)

Past Members

- Robb Krumlauf, Scientific Director, Stowers Institute for Medical Research, Kansas City, MO
- Barbara Kunz, President of Health and Life Sciences Global Business, Battelle, Columbus, OH
- Stephen Ruberg, Board of Directors, Member at National eHealth Collaborative, Senior Research Fellow at Eli Lilly

SCIENTIFIC ADVISORY COMMITTEE

The Committee consists of 17 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.
Current Committee Members

- Linda Allen, Mathematics and Statistics, Texas Tech University (1/1/09-12/31/11)
- Alexander R. A. Anderson, Co-Director of Integrated Mathematical Oncology, H. Lee Moffitt Cancer Center & Research Institute (1/1/11-12/31/13)
- Paul Bressloff, Mathematics, University of Utah (1/1/11-12/31/13)
- Chris Cosner, Mathematics, University of Miami (1/1/11-12/31/13)
- Thomas Daniel, Biology, University of Washington (1/1/10-12/31/12)
- Gerda deVries, Mathematics & Statistical Sciences, University of Alberta (1/1/11-12/31/13)
- Tim Elston, Pharmacology, University of North Carolina, Chapel Hill (1/1/11-12/31/13)
- Bard Ermentrout, Mathematics, University of Pittsburgh (1/1/09-12/31/11)
- Greg Forest, Mathematics, University of North Carolina, Chapel Hill (1/1/11-12/31/13)
- Reinhard Laubenbacher, Virginia Bioinformatics Institute, Virginia Tech (1/1/11-12/31/13)
- Naomi Leonard (Chair 2011-12), Mechanical Engineering, Princeton University (1/1/09-12/31/12)
- Andre Longtin, Physics, Center for Neural Dynamics, University of Ottawa, Canada (1/1/10-12/31/12)
- Sharon Lubkin, Mathematics, North Carolina State University (1/1/11-12/31/13)
- Michael Mackey, Director of the Centre for Applied Mathematics in Bioscience and Medicine, Physiology, McGill University (1/1/11-12/31/13)

- Paul Magwene, Biology, Duke University (1/1/09-12/31/11)
- L. Mahadevan, Engineering and Applied Sciences, Organismic & Evolutionary Biology, Harvard University (1/1/10-12/31/12)
- Steven Rust, Battelle Memorial Institute, Columbus, OH (1/1/09-12/31/11)

Past Committee Members

- Reka Albert, Physics, Pennsylvania State University
- Adam Arkin Howard Hughes, Medical Institute, Bioengineering, University of California, Berkeley
- Herb Bresler, Health and Life Sciences, Battelle Memorial Institute, Columbus, OH
- Mark Chaplain, The SIMBIOS Centre, Mathematics, University of Dundee
- Mark Denny, Biology, Stanford University
- Leah Edelstein-Keshet, Mathematics, University of British Columbia
- Lisa Fauci, Mathematics, Tulane University
- Louis Gross, The Institute for Environmental Modeling, Ecology & Evolutionary Biology, Mathematics, The University of Tennessee
- Sorin Istrail, Center for Computational Molecular Biology, Computer Science, Brown University
- Nicholas P. Jewell, Biostatistics and Statistics, University of California, Berkeley
- Kirk Jordan, IBM Computational Biology Center, Yorktown Heights, NY
- Jim Keener, Mathematics, University of Utah
- Douglas Lauffenburger, Biological Engineering, Chemical Engineering, Biology, Massachusetts Institute of Technology
- Suzanne Lenhart, Mathematics, University of Tennessee
- Mark Lewis (Chair 2009-10), Mathematical and Statistical Sciences, University of Alberta
- Gregory Mack, Environmental Monitoring and Assessment, Battelle Memorial Institute, Columbus OH
- Philip Maini, Centre for Mathematical Biology, Mathematical Institute, University of Oxford
- Claudia Neuhauser, Ecology, Evolution, and Behavior, University of Minnesota
- Karl J. Niklas, Plant Biology, Cornell University
- Lior Pachter, Mathematics, University of California, Berkeley
- Alan Perelson, Theoretical Biology and Biophysics Group, Los Alamos National Laboratory
- Linda Petzold, Mechanical and Environmental Engineering, Computer Science, University of California, Santa Barbara
- Mike Reed, Mathematics, Duke University
- John Rinzel, Center for Neural Science and the Courant Institute of Mathematical Sciences, New York University
- Stephen Ruberg, Clinical Data Technology and Services, Eli Lilly and Company, Indianapolis
- Stanislav Shvartsman, Chemical Engineering, Princeton University
- James Sneyd, Mathematics, University of Auckland, New Zealand
- Terrence Speed, Statistics, University of California, Berkeley
- John Taulbee, Epidemiology and Biometrics Division, Procter & Gamble Company, Cincinnati
- Terry Therneau, Biostatistics, Mayo Clinic College of Medicine, Rochester, MN
- Frank Tobin, Scientific Computing & Mathematical Modeling, GlaxoSmithKline
- John Tyson, Biology, Virginia Polytechnic Institute and State University
- Steven Vogel, Biology, Duke University
- Michael S. Waterman, Mathematics, University of Southern California
- Raimond L. Winslow, Center for Cardiovascular Bioinformatics & Modeling, Whitaker Biomedical Engineering Institute, and Biomedical Engineering, The Johns Hopkins University School of Medicine and Whiting School of Engineering

Committees

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.

- Irina Artsimovitch, Microbiology (7/1/11 - 6/30/14)
- Janet Best, Mathematics (7/1/11 - 6/30/14)
- Ralf Bundschuh, Physics (7/1/10 - 6/30/13)
- James Cogdell, Mathematics (7/1/10 - 6/30/13)
- Meg Daly, Evolution, Ecology, and Organismal Biology (7/1/09 - 6/30/12)
- Andrea Doseff, Heart and Lung Research Institute, Molecular Genetics, and Internal Medicine (7/1/11 - 6/30/14)
- Avner Friedman, Mathematics (7/1/09 - 6/30/12)
- Martin Feinberg, Chemical Engineering (7/1/10 - 6/30/13)
- Erich Grotewold, Plant Biology (7/1/10 - 6/30/13)
- Richard Hart, Biomedical Engineering (7/1/09 - 6/30/12)
- Tim Huang, Center for Integrative Cancer Biology (7/1/11 - 6/30/14)
- Kay Huebner, Molecular Virology, Immunology and Medical Genetics (7/1/11-6/30/14)
- Daniel Janies, Biomedical Informatics (7/1/10 - 6/30/13)
- Doug Kniss, Obstetrics and Gynecology (7/1/11 - 6/30/14)
- Stanley Lemeshow, Dean College of Public Health (7/1/09 - 6/30/12)
- Gustavo Leone, Molecular Virology, Immunology, and Medical Genetics (7/1/09 - 6/30/12)
- Shili Lin, Statistics (7/1/10 - 6/30/13)
- Thomas J Magliery, Chemistry (7/1/10 - 6/30/13)
- Stuart Mangel, Neuroscience (7/1/10 - 6/30/13)
- Elizabeth Marschall, Evolution, Ecology,and Organismal Biology (7/1/10 - 6/30/13)
- Deborah Parris, Molecular Virology (7/1/10 - 6/30/13)
- Roger Ratcliff, Psychology (7/1/10 - 6/30/13)
- Wolfgang Sadee, Pharmacology (7/1/09 - 6/30/12)
- Larry S. Schlesinger, Division of Infectious Diseases and Center for Microbial Interface Biology (7/1/09 - 6/30/12)
- Chandan Sen, Surgery (7/1/09 - 6/30/12)
- Amanda Simcox, Molecular Genetics (7/1/09 - 6/30/12)
- Parthasarathy Srinivasan, Computer Science and Engineering and of Biomedical Informatics (7/1/11 - 6/30/14)
- Don Stredney, Biomedical Applications, Ohio Supercomputer Center (7/1/09 - 6/30/12)
- Joe Travers, College of Dentistry, Oral Biology Section (7/1/11 - 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 PLAN

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 increas-

ing the diversity of future mathematical biologists.

Specifically, MBI builds and maintains diversity by the following.

1. **Boards and Advisors:** Ensure representation of underrepresented groups among the Directors, the Board of Trustees, the Scientific Advisory Committee, and the Local Scientific Advisory Committee.
2. **Science Workshops and Emphasis Programs:** Include members of underrepresented groups as members of emphasis year and workshop organizing committees and ensure broad representation among workshop participants.
3. **Training of Younger Scientists:** Ensure broad representation among postdoctoral fellows and build exposure of younger scientists to mathematical biology.
4. **Awareness Workshops:** Periodically host workshops on Opportunities in Mathematical Biology for Underrepresented Groups. The first of these workshops occurred in 2007: see http://www.mbi.ohio-state.edu/publications/annual/ar0607.pdf.

In addition, MBI will pursue the following strategies:

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

Diversity Committee

- Carlos Castillo-Chavez, Department of Mathematics and Statistics, Arizona State University (12/31/12)
- Helen Chamberlin, Department of Molecular Genetics, The Ohio State University (ex-officio)
- Joan Herbers, Department of Evolution, Ecology, & Organismal Biology, The Ohio State University (12/31/12)
- Trachette Jackson, Department of Mathematics, University of Michigan (12/31/11)
- Yi Li, Department of Mathematics, Wright State University (12/31/11)
- Maeve McCarthy, Department of Mathematics & Statistics, Murray State University (12/31/10)
- Aziz Yakubu, Department of Mathematics, Howard University (12/31/10)

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 (http://www.mbi.osu.edu/about/vlprogram.html) contains a list of Visiting Lecturers.

MBI expects to support five visiting lectures each year.

LECTURERS

- Janet Best, Ohio State
- Emery Brown, MIT
- Erika Camacho, Arizona State
- Carlos Castillo-Chavez, Arizona State
- Ricardo Cortez, Tulane University
- Isabel Darcy, University of Iowa
- Lisette de Pillis, Harvey Mudd
- Lisa Fauci, Tulane University
- Marty Golubitsky, Ohio State
- Christine Heitsch, Georgia Tech
- Fern Hunt, Howard and NIST
- Trachette Jackson, University of Michigan
- James Keener, University of Utah
- Nancy Kopell, Boston University
- Jonathan Mattingly, Duke University
- Asamoah Nkwanta, Morgan State
- Michael Reed, Duke University
- Miranda I. Teboh-Ewungkem, Lafayette College
- Talitha Washington, University of Evansville
- Abdul-Aziz Yakuba, Howard University

AGMUS Institute of Mathematics and UMET scholars at Dr. Janet Best's conference.

VLP LECTURES

This year's visiting lecturers were Janet Best (Mathematics, The Ohio State University), Trachette Jackson (Mathematics, University of Michigan), and Carlos Castillo-Chavez (Mathematical and Statistical Sciences, Arizona State University).

Janet Best traveled to Puerto Rico to give a talk on *Dynamic Systems and Mathematical Biology*. With Professor Juan Arratia as her guide, she was taken to three different Universities to give her presentation: Universidad del Este (UNE), Universidad Metropolitano (UMET), and Universidad del Turabo. These universities make up the Sistema Universitario Ana G. Mendez (AGMUS). The students at each location were very interactive. Large groups of students stayed after each presentation to ask questions and invoke lively discussions. Janet has kept in contact with several students and has talked to them in detail about opportunities at OSU. Although Janet was surprised to learn she would be giving three lectures three times, she felt this was absolutely the right way to organize the day. She said, "Possibly there could have been a single lecture broadcast to the other locations by video, but that would have been a shameful waste. These direct, personal interactions are surely a very valuable aspect of VLP lectures."

Janet Best giving a talk at one of the AGMUS universities.

Trachette Jackson gave a talk at Murray State University on *Mathematical Insights into Cancer Therapy*. During her time there, she met with faculty and discussed mathematical biology courses, NSF UBM programs, and potential collaborations. Trachette enjoyed interactions with two different groups of students. She presented some of her current research on endothelial cell-targeted anti-cancer therapies to a large audience of students and faculty.

Carlos Castillo-Chavez attended the College of Saint Rose, Albany to present *What Can Mathematics Do to Help Fight Disease?* Carlos highlighted the work of physicians like Sir Ronald Ross who pioneered the use of mathematics in epidemiology and discussed some recent applications. He interacted with undergraduates including students interested in ecology and population biology as well as in the applications of mathematics in the life and social sciences.

Visitors

LONG TERM VISITORS 2010-2011

- **Moussa Doumbai**, Mathematics, Howard University
- **Abdul Aziz Fall**, Gaston Berger University, Senegal
- **Gabriela Gomes,** Instituto Gulbenkian de Ciencia
- **Kesh Govinder**, School of Mathematical Sciences, University of KwaZulu-Natal
- **Paul Hurtado**, Applied Mathematics, Cornell University
- **Maria Leite**, University of Oklahoma
- **Dong Li**, Mathematics, Iowa State University
- **Nianpeng Li**, Mathematics, Howard University
- **Matt Miller**, Mathematics, University of South Carolina
- **Edward Lungu**, Mathematics, University of Botswana
- **Tyler McMillen**, Mathematics, Cal St. Fullerton
- **Ian Stewart**, Department of Mathematics, University of Warwick, UK
- **Barbara Szomolay**, Center for Integrated Systems Biology, Imperial College, London
- **Satoshi Takahashi**, Zayed University
- **Carl Toews**, Mathematics, Duquesne University
- **Shari Wiley**, Mathematics, Howard University
- **Abdul Aziz Yakuba**, Math Dept. Chair, Howard University
- **Tunde Tajudeen Yusuf**, Federal University of Technology Akure, Nigeria

LONG TERM VISITORS 2011-2012

- **Edward Allen**, Math & Stats, Texas Tech University
- **Linda Allen**, Math & Stats, Texas Tech University
- **Debashish Chowdury**, Physics, India Institute of Technology
- **Adnan Khan**, Mathematics, Lahore University
- **Peter Kramer**, Mathematical Sciences, RPI
- **Vlastimil Krivan**, Mathematics, University of South Bohemia
- **Tom Kurtz**, Mathematics, University of Wisconsin-Madison
- **Reinhard Laubenbaucher**, Bioinformatics Institute, Virginia Tech
- **Dong Li**, Mathematics, Iowa State University
- **Kang-Ling Liao**, National Jiao Tong University, Taiwan
- **John Mattingly**, Mathematics, Duke University
- **Anastasios Matzavinos**, Mathematics, Iowa State University
- **Scott McKinley**, Mathematics, University of Florida
- **John McSweeney**, Mathematics
- **Greg Rempala**, Biostats/Bioinformatics, Georgia Health Sciences University
- **Joaquin Rivera-Cruz**, Mathematics, Colgate University
- **Elissa Schwartz**, Mathematics, Washington State University

- **Kajetan Sikorski**, Mathematical Sciences, RPI
- **Ian Stewart**, Mathematics, University of Warwick
- **Brandy Stigler**, Bioinformatics Institute, Virginia Tech
- **Peter Thomas**, Mathematics, Case Western Reserve University
- **Yang Wang**, Mathematics, Hangzhou Dianzi University
- **Zhi An Wang**, Applied Mathematics, Hong Kong Polytechnic University
- **Shari Wiley**, Mathematics, Howard University

COURSE RELEASE 2010-2011

MATHEMATICS

- Ching-Shan Chou
- Bo Guan
- Yuan Lou
- Avner Friedman
- Chiu-Yen Kao
- Joe Tien

STATISTICS

- Jason Hsu
- Laura Kubatko

ELECTRICAL AND COMPUTER ENGINEERING

- Kevin Passino

COURSE RELEASE 2011-2012

MATHEMATICS

- Janet Best
- Avner Friedman
- Yuan Lou
- Chuan Xue
- Ching-Shan Chou
- Bo Guan
- Joe Tien

STATISTICS

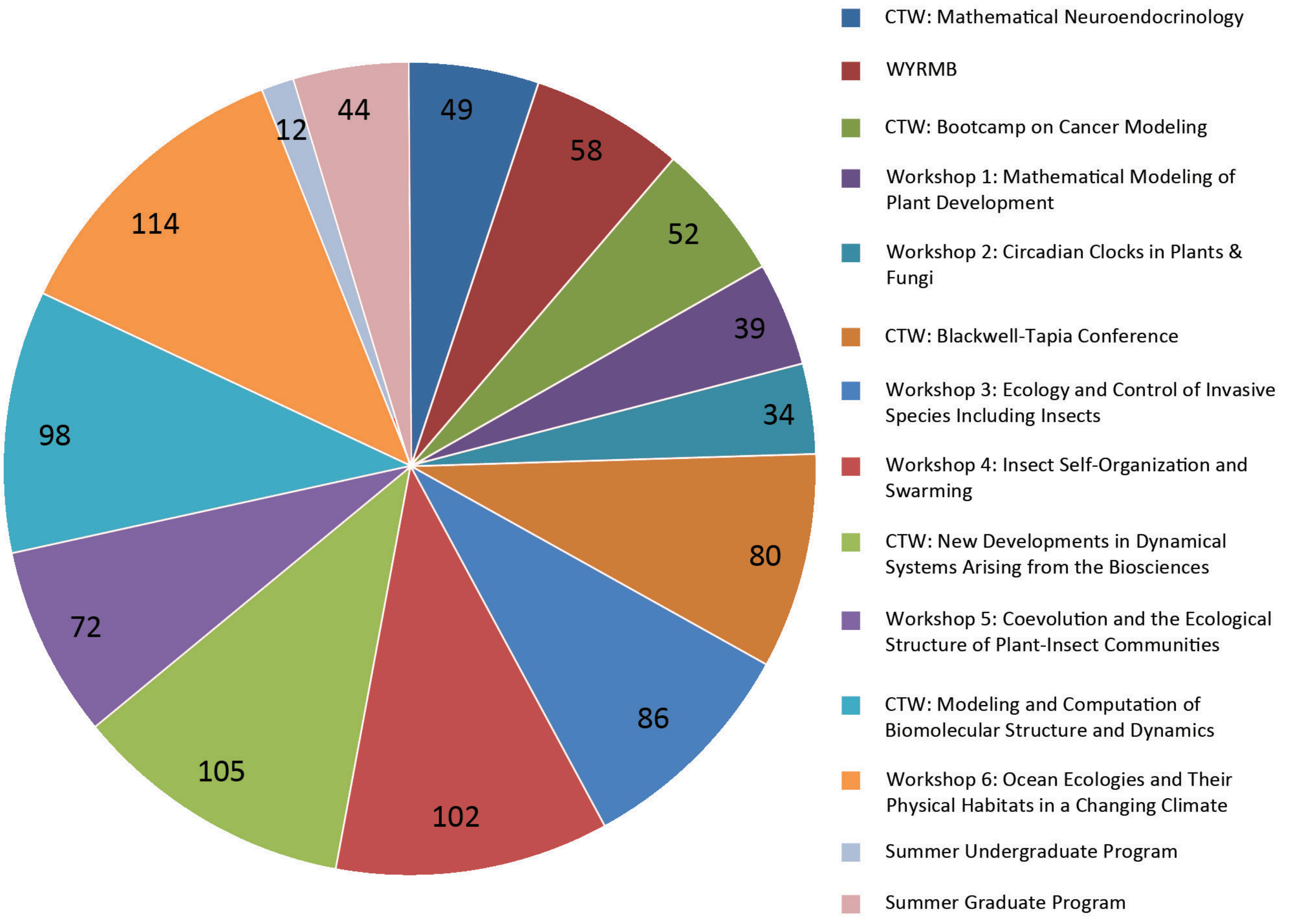
- Radu Herbei
- Tao Shi
- Xinyi Xu
- Shili Lin
- Joe Verducci

ELECTRICAL AND COMPUTER ENGINEERING

- Terry Conlisk
- Kevin Passino
- Srinivasan Parthasarathy

PROGRAM PARTICIPATION

The chart below shows the total number of participants for each MBI event during the 2010-2011 emphasis year. **The total number of participants this year was 945.**



Evolution, Synchronization, & Environmental Interactions: Insights from Plants & Insects

ORGANIZING COMMITTEE

- Vincent Gutschick (La Cruces Academy)
- Daniel Forger (Mathematics, Michigan State University)
- Mark Lewis (Biology, University of Alberta)
- Scott Nuismer (Biological Sciences, University of Idaho)
- David Rand (Warwick Systems Biology Centre)
- David Sumpter (Mathematics, Uppsala University)

Myriad influences shape the patterns of evolution, timing, behavior and ecology of living organisms. These influences range from biochemical cues to configurations of temperature, space and light, to interactions with other organisms. This one-year program focuses on connecting influence to pattern for processes involving plants and insects.

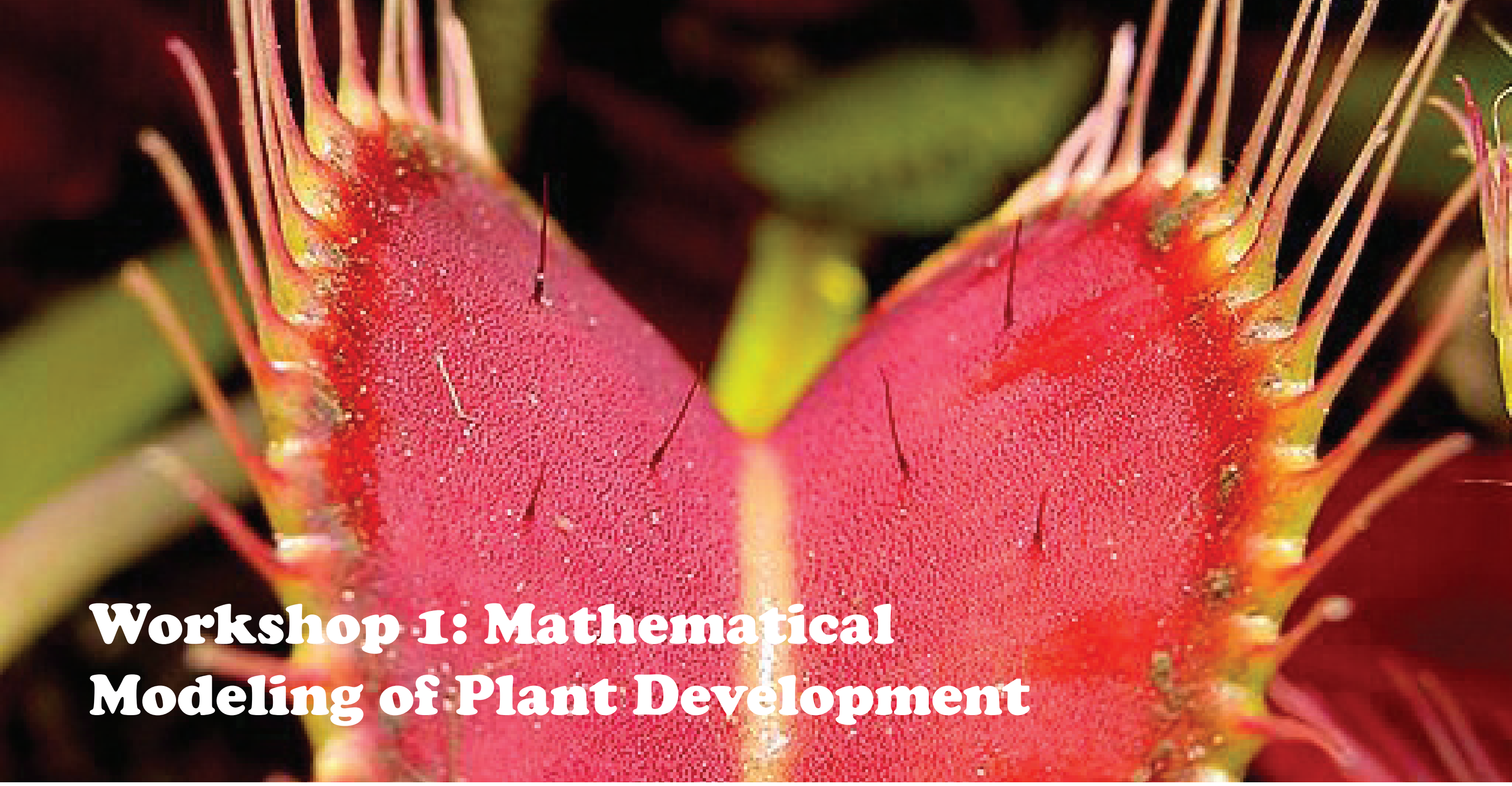
How do biotic and abiotic influences affect patterns of plants and insects? We investigate this complex question quantitatively, by focusing on specific areas where there has been recent growth, simultaneously in mathematical and statistical theories and in biological data and experiment. We propose to couple the mathematics and biology in new ways, allowing for innovative growth of both science and mathematics.

The year is based around the following workshops: (i) Mathematical modeling of plant development, (ii) Circadian clocks in plants and fungi, (iii) Insect self-organization and swarming, (iv) Ecology and control of invasive species, including insects, and (v) Coevolution and the ecological structure of plant-insect communities. Our mathematical investigation of these processes will rely upon a diverse array of quantitative theory, including geometry, control, optimization, pattern formation, spatial dynamics, evolution and data-model interaction.

The plant development workshop will connect biochemical mechanisms to geometric patterns, while simultaneously investigating the selection pressure for the geometric patterns. Circadian clocks will be evaluated both from the perspective of design features for feedback and control, and of robustness of these features to perturbation. Insect self-organization and swarming will employ dual perspectives of emergent self-organization properties arising from individual interactions, and optimal design of artificial swarms using diffuse (decentralized) information with implications for robotics and decentralized computer algorithms. Biological invasions will be understood, not only in terms of predictable forecasting of future invasions, but in terms of optimal control of the invasion processes. Finally, the physical and behavioral mechanisms involved in coevolution of plant-insect communities will be understood in terms of fitness advantages incurred evolution and adaptation.

Thus the underlying feature throughout the workshops is simultaneous investigation of mechanism and optimality: What mechanisms give rise to observed patterns? What is the fitness or optimality associated with observed patterns? It is through this simultaneous study of mechanism and optimality in plants and insects that the workshops will provide general insight to the processes of evolution, synchronization and environmental interactions.

The goals of the year program are (i) to develop, analyze and apply new mathematical models for processes of evolution, timing, behavior and ecology of living organisms that are tailored to investigate both mechanisms underlying the processes and optimality of associated patterns; and (ii) train interdisciplinary quantitative researchers at a variety of levels (graduate, postdoctoral and faculty) in the area of evolution, synchronization and environmental interactions for biological systems.



Workshop 1: Mathematical Modeling of Plant Development

SEPTEMBER 27 – OCTOBER 1, 2010

Organizers: Vincent Gutschick (La Cruces Academy), Karine Chenu (Queensland Alliance for Agriculture & Food Innovation), Michaël Chelle (INRA), and H.G. Lyn Jones (University of Dundee)

Report written by Richard Gejii, Rachel Leander and Dan Siegal-Gaskins

MONDAY, SEPTEMBER 27
WHY ARE WE MAKING MODELS?

Modeling tree development: An overview of open questions specific to fruit trees
Evelyne Costes (UMR 1098 DAP, INRA)

Although fruit tree development occurs at many different scales, Dr. Costes chose to focus on the scale of an individual tree. In particular she explored how the topology and geometry of apple trees change over many years. Using data collected from apple trees she constructed a model with mechanistic and stochastic components. This model enabled her to identify developmental patterns in tree branch, leaf, and flower development that were implicit, though hidden, in the data. She identifies rules that govern the succession of growth units and the location of branching. Current challenges include the introduction of environmental and genetic variability through added stochasticity, functional-structural plant modeling (FSPM), or by modeling cellular and molecular mechanisms. Dr. Costes concluded that, although patterns and structural properties of tree development had been revealed, most of the underlying physiological and molecular mechanisms remain unknown. However, her model could be used to validate models of tree development at the molecular scale and to construct multiscale models. She showed a video of confocal microscopy images that track the development of cell shape and volume; her group is seeking ways to integrate the findings into their models.

Combining multiple modeling approaches to design plant ideotypes for specific climates
Thierry Simonneau (UMR 759, LEPSE, INRA)

Dr. Simonneau discussed how various types of models can be combined to simulate environmental variation in gene expression. He emphasized the value of very simple representations of the environmental effects, enabling high-throughput phenotyping. Some congruences in temperature responses among diverse processes and phylogenetically-diverse plant species were striking. Model predictions were confirmed in experimental tests, introducing one quantitative trait locus (gene) into a parental line. Dr. Simonneau highlighted the value of open-source sites such as OpenAlea, which allow modelers to integrate many different types of models. He also used simple ODE models with normalized environmental and genotypic parameters. He concluded that while it is possible to merge genetic analysis with current models, more research is needed on the mechanisms by which quantitative trait loci (QTLs) determine phenotypes. Diverse questions and discussions followed his talk and covered the specific findings as well as extensions to evolutionary topics.

Group Discussion: What model for which purpose?

Models were classified as being statistical/empirical or mechanistic, bottom up or top down, and simple or complex. Models were recognized as tools that enable us to make predictions, summarize/analyze data, estimate parameters, and test hypotheses.

At which scale should we model plant-climate-pathogen interactions to find new levers in pest management-Is the phylloclimate a key variable?
Michaël Chelle (UMR1091 EGC, INRA)

Dr. Chelle discussed the modeling of plant-climate-pathogen interactions for pest management. In particular, he addressed the great range of scales at which these interactions take place. At the large scale, interactions between the canopy and its environment are known to be critical; however, Dr. Chelle argued that phylloclimates, i.e. the climates perceived by individual organs, are of equal importance. At such small scales variations in temperature, for one, are pronounced, while at larger scales a variety of feedbacks greatly reduce the variation. Dr. Chelle described the use of 3-D process-based models for transport of radiation, heat, and mass, and the mathematical methods necessary to solve the equations efficiently. Such models are useful for designing crop management and for developing plant ideotypes that yield canopies with multiple modes of defenses against pathogens. En route to such uses, models are also needed to estimate conditions at fine scales where measurements are wholly impractical. He presented considerations of evolutionary responses of plants to pathogens and of the effects of climate change (temperature) on potential disease impacts. He noted the emergence of plant modeling platforms, including OpenAlea. Finally, he detailed a variety of mathematical questions, including robust coupling of nonlinear models, solving large-matrix models, performing fast Monte-Carlo analyses, and using multi-criteria assessments. He stressed that intrinsic biological variability differs from uncertainty and error. In the question period, the co-adaptation of pathogens was noted.

Simulating grass morphogenesis with a self-organizing cybernetic framework
Abraham Escobar-Gutierrez (UR4 P3F, INRA)

Dr. Escobar-Gutierrez presented the view that models provide frameworks for thinking, for hypothesis testing, and for knowledge integration. Motivated by the agricultural usage of grasslands (which cover 30% of the EU and are basically domesticated ecosystems), and the viewpoint that a grass individual is like a flock of leaves, he developed a model of plant structure and functioning where each added plant leaf alters the phytomer demography. The model, based on L-system modules, is necessitated by the absence of a known simple genetic regulatory network. It enables one to ask and answer questions concerning plant development. Using this model he was able to show how leaf elongation is affected by environmental determinants and how the elongation dynamics affected the structure of the plant tillers - the longer the leaves the lower the number of tillers. The system displays a lack of controllability, in the sense that it is impossible to predict final plant architecture from initial conditions, environmental inputs and developmental rules. Uses of the model include decision support and grass breeding.

Strigolactones and long-distance transport of polar auxin
Christine Beveridge (University of Western Australia)

Dr. Beveridge discussed the hypothesis that a group of plant hormones known as strigolactones that inhibit branching may also affect the transport of the plant growth hormone auxin through stems. Modeling is seen as a key to developing and testing the hypotheses that must be elaborated. Auxin is known to maintain strigolactone levels and evidence suggests that strigolactone may affect auxin transport in roots. She generated a model of auxin transport through the stem at the mm scale, tracking individual auxin particles in a Lagrangian framework. A major aim of the model was to define the properties of the polar carrier-dependent transport system. The model enabled investigating how changes in auxin transport at the molecular level could affect the auxin transport wave. She concluded carrier availability was critical for fast auxin transport and, moreover, strigolactone affects local loading but not long-distance transport. Furthermore, auxin deficiency moves at too slow a rate to carry the signal of plant decapitation that affects bud break (breaking of apical dominance). In response to a question, Dr. Beveridge offered that the likely signal is the change in turgor pressure.

Report of Group Discussion

Each of four breakout groups had a rapporteur present their results. In one group, the fundamental question was, “What is a model?” with responses ranging over many types of models and teleological viewpoints. Models were seen as essential in basic mechanistic understanding of coupled processes as well as for application of diverse knowledge, including the burgeoning set of information in the “-omics” (genomics, proteomics, metabolomics, …). Within modeling, the impacts of errors and natural variability are too often missing. In the report of the second group, it was noted that biology and mathematics (mathematical modeling) meet as biology includes processes (without inherent assessment of importance) while mathematics exclude processes. The report emphasized the challenges in overfitting models, calibrating them, and extrapolating them beyond the original data. Value was seen in getting standardized modules. The third group cited models as the way to translate measurement to understanding, and they emphasized that one must articulate what a model must predict, or else one is not ready to model. Models are also viewed as useful for delimiting or replacing many expensive experiments. The group noted that we are sometimes required to generate models that cannot be verified in real time, as in climate change, and this necessitates careful model intercomparisons. A strong criterion for judging models in such intercomparisons is that they must reproduce results where analytical solutions exist to notional conditions. The final group reaffirmed that models are tests of our understanding of biological systems. They also integrate over scales of space and time, including scales where we cannot make measurements, such as detailed spectral balances (red: far red) at all canopy locations. The group noted that sensitivity analysis of models is important. A plenary discussion ended the afternoon. One item brought up is that models are as variable in their natures as are plants; a typology of models would be useful. The group discussed the optimal degree of complexity of models (e.g., make a complex model and then simplify to an acceptable level of accuracy?). The problem of limited verification of models over large scales was discussed, with the example of eddy covariance (EC) as verification of flux models. A point was made that, even with the disturbingly pervasive errors in energy balance in EC, the diurnal and seasonal variations are more reliable and provide good criteria for assessing models. In the spirit of the scientific method, it was offered that models are not to prove us right but to show us where we are wrong.

TUESDAY, SEPTEMBER 28
MODELING THE IMPACT OF THE ULTIMATE DRIVERS - GENES, BIOCHEMISTRY, AND ENVIRONMENTAL EFFECTS (PART 1)

Functional-structural plant modeling: a new versatile tool in plant modeling
Jan Vos (Wageningen University)

Dr. Vos introduced functional-structural plant modeling (FSPM) as a way to model the interactions between the function and structure of plant. He showed that by using a modular model based on phytomers, it is possible to model how plants respond not only by changing their processes but also their structure. Using wheat as an example he outlined the steps to construct and parameterize an FSPM. The model incorporated a hierarchy of processes and was implemented using L-systems. To the structural rules he added a number of physiological and radiative transport processes. He raised the important point that the resultant details of the local radiative climate are essentially impossible to obtain by experiment. Ramifications of the work include inverse modeling to retrieve canopy parameters. The model has been applied to diverse crops, including kiwis, roses, and wheat. Dr. Vos asked the critical question, “What do models really prove?” and he elaborated on 4 tests in the wheat study, only one of which had a clear answer from the model. He concluded that the FSPM is a useful tool, with promise when combined with systems biology.

Poster Presentation
Eric Casella (UK Forestry Commission)

Eric presented a poster on using ground-mounted scanning LIDAR to estimate gap fraction in forest canopies – an important parameter in models for estimating overstory and understory light interception and photosynthesis. In contrast to photographic methods, LIDAR estimates are not sensitive to sky conditions. They do require measurement times on the scale of a number of minutes; consequently, study is needed on the effects of wind-induced leaf movements on the accuracy of the results.

Functional whole plant modeling: the missing link between molecular biology and crop improvement?
Karine Chenu (Queensland Alliance for Agriculture and Food Innovation)

Dr. Chenu presented her group’s work to model the simultaneous contributions of genes, the environment, and crop management to improving crop productivity. Using the APSIM modeling platform, they are developing robust explanatory models for plant phenotype as driven by genotype (and environment). Phenotype is compactly described by a set of parameters, a technique that also reduces the context-dependency of phenotype descriptions (dependence on unique features of any given environment). Her group’s models simulate the full pathway from genotype to crop, generating estimates of final yield. The second part of her talk was devoted to modeling the effects of genotype (described as quantitative trait loci) on key parameters of leaf expansion rate as responding to temperature, humidity, and water potential. In the third part of her talk, modeling was carried all the way to strategies of plant breeding, estimating yield for different populations in various environments, with the combined use of the APSIM crop model and the QUGENE breeding model. In the fourth and final part, she described how environmental complexity could be reduced to two dimensions and results in simple environmental characterizations useful for breeding programs. In the question period following her talk, Dr. Chenu clarified that nonadditive (interactive) effects of multiple genes could be accounted in the model, and that the physical process of energy balance is not yet accounted. She noted that some plant breeders are quite receptive to using the models to guide breeding efforts.

Group Discussion: How can plant models use the large amount of "-omics" data (genomics, proteomics, metabolomics) that is now available to answer agricultural and ecological questions and problems?

Participants discussed how models could be used to identify genes that control important traits, and to determine the mechanisms by which phenotypes are expressed once the responsible genes have been identified. One group addressed the question, "Is it a problem to make people aware of the value of models?" By the end of the workshop, this and related issues led the group to propose collaborating in writing a position paper on the value of models for submission to a major journal. It was emphasized that the use of models requires considerable background on the part of the user, so that potential users need be given immediate incentives by showing the ultimate utility of models. Complexity or comprehensiveness in models has a place in conceptual development but not in final model usage. Models tell us what is important in a welter of phenomena and parameters, and they are necessary where experiments are completely impractical (resolving intermediate details). New concepts emerge from models. Regrettably, non-modeler biologists still pay little attention to models, forgoing invited participation in meetings. Systems biology absolutely needs models. In conclusion, plant models were viewed as the best hope to close the gap between the huge data flows and major agricultural and ecological questions: the latter questions are well-posed and documented, the date exist, and the QTL approach calls for –omics data at all scales. There is a need to link laboratory model plant species to crop systems.

Using functional-structural plant modeling to study, understand and simulate fruit tree physiology, architecture, growth and production responses to changes in genetics, environment and management
Ted DeJong (UC, Davis)

Dr. DeJong discussed the L-PEACH model, which is an example of an FSPM that incorporates physiological, architectural, growth, and productivity responses to environmental stimuli and management practices. The model is very complex and computationally intensive, but DeJong made forceful arguments about the value of comprehensive models as tools for learning and for recognizing emergent properties such as spatial patterns of phloem transport properties. He demonstrated the models ability to predict a variety of quantitative tree characteristics including the hourly leaf respiration rate and the leaf weight as well as the tree's structure in both normal and drought conditions. Several stunning computer animations of tree development under various management strategies were shown, reinforcing DeJong's point that visualizations are potent in gaining the interest of non-modeler biologists. In the question period, it was pointed out that considerable insufficiency in the model's description of belowground processes and in stomatal control of gas exchange in leaves can be remedied with extant (sub) models. Also, the lack of accounting of effects of adjacent trees on light interception by the tree in question could be addressed with periodic boundary conditions at the simplest. One participant noted that he has used the model for optimizing pruning as a management tool.

Simplifying modeling assumptions in the GreenLab models and methods for parameter identification for trees
Veronique Letort (Ecole Centrale of Paris)

Dr. Letort showed how to model tree growth with GreenLab, a dynamic system of plant growth. Three criteria guide modeling in her group: keep it simple, keep it on the same scale as measurements, and keep it generic (use a minimal set of processes). Parameters of the processes are derived by fitting. A goal is to develop optimal control for crop management. She presented a model of organogenesis in fruit trees, formulated on an intermediate or meso-scale in resolving time, spatial structure, and state space (physiological age). Tree structure was constructed inductively, with substructures (buds, leaves, etc.) at each new time step deduced from those at the previous step, thus reducing the computation time from exponential to quadratic. Organogenesis was modeled stochastically. Using a parameter fitted meso-scale model, her simulations show that ontogenetic gradients, fructification, and branching rhythms may be emergent properties of the ratio of biomass production to organ demand (Q/D). She presented examples of simulations on Mongolian Scots pine and Cecropia, the "Arabidopsis of trees." Simulations can be extended to large landscapes. Measurements have been pursued on real trees, disassembling them. In the question period, participants asked if Q/D is as potent a predictor of fructification as claimed and also if it predicted fructification for the whole tree vs. individual branches.

Using models of plant hydraulic function to predict gas exchange, growth, and survival in response to environment and ontogeny
John Sperry (University of Utah)

Dr. Sperry explained that models of plant hydraulic resistance are useful because they provide mechanistically anchored predictions of plant gas exchange and survival in response to environmental stress and ontogeny. He reviewed the dynam-

Wendy Silk (UC Davis)

ics of water transport in plants and then presented a soil-plant-atmosphere-continuum model that was used to predict the sensitivity of plant gas exchange and survival in response to water stress. He discussed an allometric model that was used to predict water use and productivity as a function of plant size and functional type. The latter model was found to be biologically unrealistic in detail, leading to a merging of models in a collaborative effort between the originators and Sperry. The new model used a symmetric branching network for the xylem vessels that transport water, generating a column with constant xylem area. A series of scaling arguments lead to predictions of ultimate growth rate as proportional to the ¾ power of mass, significantly different from the earlier allometric model. Further refinement was based on the finitude of height for real trees and on the difference in biomechanical constraints between short and tall plants. The tree growth rate is then seen to be in proportion to mass to an exponent that ranges from 0.55 to 0.72, averaging 0.65. Forgoing simple math, he than presented results of a numerical solution of the biomechanical and transport considerations, including details of trunk structure such as partial conversion of xylem to non-conducting heartwood. Predictions were good for maple but not for oak, where recurrent xylem caviation (loss of conductivity) occurs and where the fraction of growth allocated to roots vs. shoot vary with size. Sperry presented a yet more complete model that accounted for variation of flow resistances with stress level in xylem and in soil. The model made good predictions of whole-plant water transport (transpiration) and the necessary patterns of control of water use at the leaf level by stomata. Applied to the dramatic dieback of conifers in the Western US a few years ago, the model yields the interpretation that water stress did not cause catastrophic xylem cavitation; rather, it induced stomatal closure with resultant heat stress that made trees vulnerable to bark beetles.

Report of Group Discussion

The day ended with reports of three discussion groups, elaborating on the topic of if and how models are useful in assimilating the vast data flow in the –omics research. The assimilation into useful concepts was typed as a dream but a dream worth pursuing. Data mining could be of great value. Educating a new cadre of students is necessary, even as specialization is increasingly demanded. We must get our questions onto the agenda of the funding agencies. Aiding in our use of data, and conditioning it, is the reduction of complexity at higher levels such as the ecophysiological. There are then some success stories, linking genes to many higher functions in Arabidopsis and even to wind resistance in trees. Modular models or theories, à la L-systems were viewed as efficient. A necessary step in using –omics data is the construction of gene regulatory networks. There is a need for equilibration of sorts – omics has lots of data but no models, crops have models but much less data. Crops also lack sufficient genetic data, forcing the use of non-crop model plant species to understand gene function (more remotely then). Larger challenges arise in studying global change, which involves far more species than our crops. On the other hand, it was noted that we don't necessarily need to know the details of how a gene acts (in metabolic pathways and regulatory networks) in order to see its effects on phenotype and ultimate crop performance. The utility to modelers of the genetic and other –omics databases must be raised with much more metadata beyond the simple genetics. From considerable experience, modelers can help recast questions asked by –omics researchers, such as their search for, say, a gene for drought tolerance, when we know that there are many interacting processes. Modelers are also aware of the dependence of gene action of the whole environment. Collaboration of modelers and –omics researchers is thereby necessary. A final note was the difference in roles for simple models (addressing one goal) and complex models (exploration to develop concepts). Complexity was resolved into various types – conceptual complexity, mathematical complexity, and computational complexity, and these are not closely connected. Several participants expressed optimism that we will ultimately comprehend the entire series of links, from genes to performance.

WEDNESDAY, SEPTEMBER 29
MODELING THE IMPACT OF THE ULTIMATE DRIVERS - GENES, BIOCHEMISTRY, AND ENVIRONMENTAL EFFECTS (PART 2)

Using growth kinematics to understand gene functioning for adaptation to a changing environment
Wendy K. Silk (Dept. of Land, Air, and Water Resources, UC Davis)

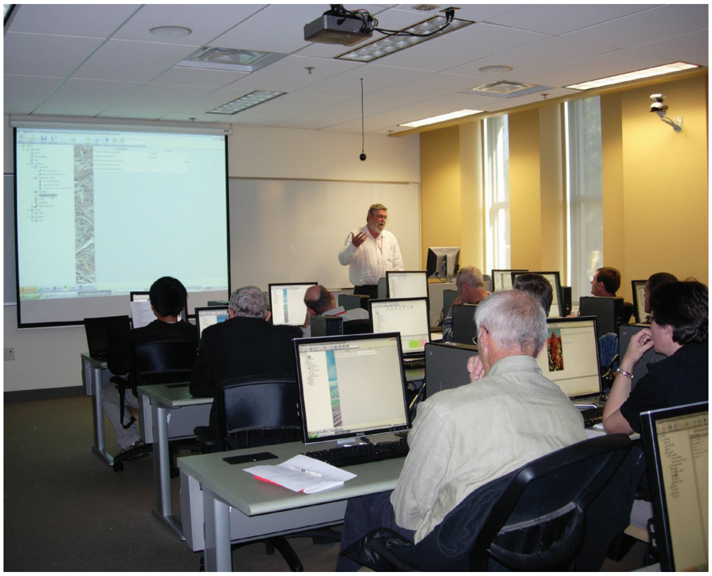
Dr. Silk used her work with kelp to illustrate how the analysis of plant growth is critical for understanding adaptation. She illustrated the value of using a Lagrangian frame that moves with the tissue apex, that of the shoot or of the root. She developed the basic equations of continuity and the process-based constitutive equations such as those for water potentials that sustain growth. Dr. Silk then used an elastic-buckling growth model to explain how the structure of kelp fronds vary with their environment (i.e., the fronds are wide and ruffled in calm waters to avoid clumping but smooth and narrow in turbulent waters to reduce drag). Specifically, her model showed that ruffles can be explained by the fact that growth is more rapid along the edge of the kelp blade. Because the blade is thin, it bends or ruffles rather than stretches to attain the state of minimal energy. Dr. Silk also discussed how growing plant parts structure their environment, such as the concentration profiles of nutrient and exuded chemicals. She then performed an original and stirring ballad about the journey of a group of laboratory researchers atop a growing and then through a transitioning plant. Finally Dr. Silk discussed net deposition or biosynthesis rates and suggested that growth analysis could be a powerful tool for understanding gene function. Specifically after obtaining a growth velocity field and determining the spatial pattern of relative gene transcript and product density one could calculate the transcript production rate and use the growth trajectory to determine the time course of translation and transcription. In the discussion that followed, she clarified that the vacoular expansion needs to be accounted at the cellular level but not at the bulk level.

Model-assisted integration of physiological and environmental constraints affecting the dynamic and spatial patterns of root water uptake from soils
Xavier Draye (Universite Catholique de Louvain)

Draye's work was motivated by a desire to understand the role of the root system architecture (RSA) at different levels of water availability and in different soil textures. The study is hypothesis-driven and seeks to identify optimal RSA, working ultimately from genetic bases, and practically from fundamental parameters of root axial and radial hydraulic conductivities and soil hydraulic conductivity. These conductivities are dynamic, varying with soil water potential and with induced vessel cavitation, thereby generating rich 3-D patterns. Dr. Draye began with a mathematical formulation of the genetic constraints on the RSA based on genetic data. By using a 3D model of the RSA, he was able to quantitatively show that root water uptake varies drastically with water status and soil type, variously affording control of water uptake to either RSA or soil. He concluded that models which combine root biology with soil physics will help researchers to make informed decisions about which features of the RSA can be altered to improve drought tolerance, before they begin the costly process of implementing these changes and testing them in the field. In the discussion period, it was noted that it is complicated to test the predictions of the model. He also indicated how the many genetic parameters can be reduced to a few geometric and topological parameters that determine the net radial, axial, and soil conductivities. He was asked if the model also considered mineral uptake and he noted in response that pollution control is one of the model's aims. The last part of the discussion centered on the utility of partial root drying, both as subject to modeling and as effective in inducing increased water-use efficiency (rarely, was the answer).

Demonstration: Agricultural Production Systems Simulator (APSIM)
Greg McLean and Karine Chenu (Queensland Government)

APSIM contains a suite of modules enabling the simulation of systems covering a range of plant, animal, soil, climate, and management interactions. The demonstration included an exercise in which participants simulated the dynamics of genotype-management-environment interactions (GxMxE). Each participant used a separate PC as a terminal for access to APSIM. Drs. McLean and Chenu reviewed the detailed descriptors of the system comprising soil, plant genetic traits, and management practices (planting date, irrigation, etc.). Choosing a geographic location and a crop, the participants then accessed an extensive data file with both fixed parameters such as soil type and variables that they could set (e.g., planting date, genotype). The objective was to make choices that optimized final yield. APSIM allowed display of a variety of dynamic variables, such as total and reproductive biomass over time. The trajectories afforded insight into how yield might be optimized.



Leaf to forest: 3D modeling for quantifying and understanding radiation interactions in vegetation
Mathias Disney (University College of London)

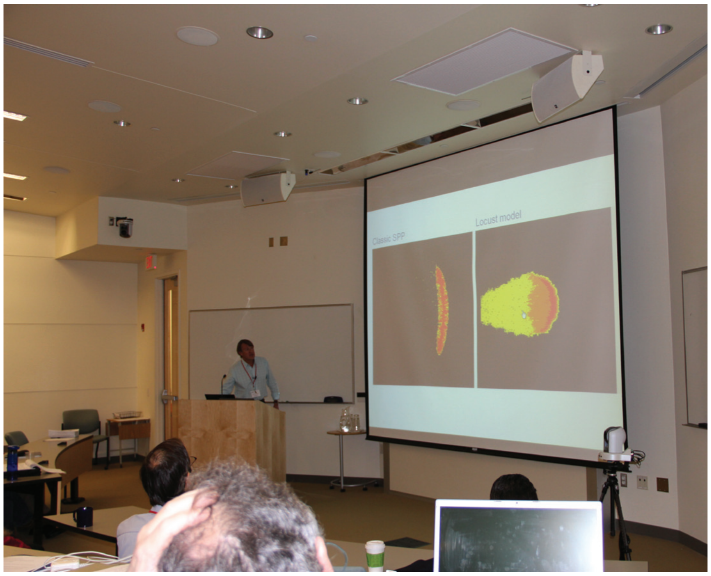
Understanding the radiation regime in vegetation canopies is necessary for understanding canopy properties measured remotely, particularly vegetation state (ecosystem productivity, carbon accumulation) and dynamics (phenology, response to changing climate and natural and anthropogenic disturbances), across a range of scales from leaf-level (cm and below) to global. Dr. Disney works in an extensive collaboration, developing and testing models of radiative transfer in plant canopies and testing them against field measurements, both satellite and ground-based . He offered the humorous but real caution that only modelers believe their hypotheses and only experimenters doubt their findings. He presented a detailed 3D approach to modeling canopy scattering, based on Monte Carlo ray tracing and 3D structural canopy models, and he noted comparisons with models of various scales and types of computational approximations – analytical models, voxel models, radiosity models, etc. Models must replicate analytically-solvable cases and are also compared to detailed real-world cases. They also must be used in a data-assimilation mode, correcting their parameters over time to refine their agreement with observations. Model corrections consistently in one direction indicate conceptual flaws. Models run in inverse mode enable resolution of fine canopy structure, particularly if use is made of multi-angle observations. The complex models avoid artifacts caused by shadows on the landscape and problems of signal saturation in dense canopies. A new approach of spectral invariants helps with the latter problem, while offering the insight that it may be impossible to separately resolve canopy structure and biochemical attributes such as chlorophyll content. Phase-sensitive signals such as LIDAR might be interpretable for canopy structure, with the use of 3-D models. Dr. Disney noted some practical applications, including studying the impacts of fire in savanna ecosystems. In the discussion period, challenges were noted in inferring connectivity of structures from multiple-scattering information and in estimating ecosystem productivity with coarse time steps afforded by high-resolution satellite imagery.

Some scaling problems in remote sensing
Hamlyn Jones (Plant Science Division, University of Dundee at SCRI)

Dr. Jones noted that problems arise in both temporal and spatial scaling, then focusing on spatial scaling in his talk. He discussed a number of problems faced by those who work with large spatial scale imagery. For example, the aggregation of image data into low-resolution pixels results in irretrievable information loss. However, if the pixel size is too small, irrelevant information, such as that relating to individual leaves, is retrieved, and data volume may also become too large. Dr. Jones spoke about the practical impact of changing the scale of observation, and detailed the non-linearity inherent in the interpretation of some types of satellite imagery. The non-linear relation that exists between Leaf Area Index (LAI) and the conventional Normalized Difference Vegetation Index (NDVI) illustrated this point. Dr. Jones noted that integration of phenomena at larger scales can reduce nonlinearity problems in some cases, such as light responses of photosynthesis on going from leaf to canopy. Errors in observations compound the scaling errors, particularly for inverse models. He concluded by discussing the serious consequences of ignoring scaling problems, including errors in biomass estimation, plant function estimation, and land-surface classification. The discussion following Dr. Jones' talk covered a number of topics. It was suggested that homogenization methods for nonlinear functions as used in materials science might be applied in remote sensing. Multiangle sensing also can reduce artifacts, such as from shadows. Inclusion of more phenomena in models increases computational load, which is not a serious problem, but the (satellite) observations then have a longer return time. High resolution can exacerbate instabilities in inverse models, thereby hiding important information.

Group Discussion

One topic was the proper scale of information for driving process models. Reduction is merited to only the parameters to which model outputs are significantly sensitive; if parameters are strongly correlated, one must go to another level. Too much input information may lead to channel overload and loss of information in the output. Dealing with stochasticity generated another thread of discussion. Our models are commonly deterministic, so that stochasticity in inputs is readily handled by rerunning models over a distribution of inputs. In rare cases, nonlinear models may generate stochasticity (chaos) internally; even these may collapse to greater determinism such as occurs in bulk diffusion phenomena, or, generally, with dissipative structures that collapse trajectories to a small region of phase space. Debugging an inherently stochastic model takes longer than debugging a deterministic model. Stochasticity in plant and canopy structure is natural; a model with exactly repeated architecture leads to unrealistic singularities in the bidirectional reflectance distribution function. The challenge of taking into account uncertainties in both data and models was briefly discussed. The session closed with a discussion of time steps. L-systems can have problems with incorrect time steps. Coupling models that run on different time steps is a challenge, sometimes met by using varying time steps (as between day and night) or by using event-driven calculations – the time step is set by events.



THURSDAY, SEPTEMBER 30
HOW DO WE ANALYZE THE RESULTS? IMAGE ANALYSIS, OPTIMIZATION, INVERSE MODELING

OpenAlea
Jean-Christophe Soulie and Michaël Chelle

OpenAlea is an open-source modeling platform developed by INRIA in France specifically for plant modeling. The platform is meant to alleviate the effort of building one's own model or submodels, instead using interoperable software. It addresses the multi-disciplinary nature of many research questions and the low reusability of most models, which are written in different languages on different operating systems and with different data structures. OpenAlea promotes sharing of software and tools and can lead to increased model quality. Python is used as the language to "glue" the modules and itself offers many library functions. Programming is visual, using Python's GUI toolkits. The platform works in Windows, Linux, and Macs. Dr. Soulie closed with a demonstration of OpenAlea on representative tasks. In the discussion, Dr. Michaël Chelle noted that his Caribu model of canopy microclimate is incorporated in OpenAlea, saving development time for other modelers.
Allocation dilemmas in plants

Jan Kozlowski (Institute of Environmental Sciences, Jagiellonian University)

Dr. Kozlowski began by describing how the members of even a single genus, Veronica, have a wide variety of life forms – annuals, biennials, sub-shrubs, and shrubs. He then went on to show how optimal control theory can be used to predict the way plants allocate energy among different components, and how the optimal allocation strategy varies with a plant's physical structure, life cycle, and environment. For annuals described purely in terms of body mass, the optimum reproductive yield occurs with bang-bang or instantaneous switching to reproduction, as shown by constructing a Hamiltonian and solving for the optimum with a Pontryagin maximum principle. More general cases are treated with dynamic programming or other numerical methods. Nonlinearity of growth rates in biomass causes the optimal switching to be distributed in time. Perenniation is seen to require a sufficiently high probability of survival. Storage in annuals can be optimal if storing organs are less vulnerable to herbivory. Storage is critical in perennials. At a critical size, its optimal use shifts between reproduction in one year vs. support of vegetative regrowth in a succeeding year. Dr. Kozlowski recounted a series of researchers' insights on the optimality (or non-optimality) of multiple reproductive episodes (poylcarpy) vs. a single episode (monocarpy). He discussed why woody tissue is useful in perennials, as a conjunction of survival probability and the concavity of the productivity curve. He illustrated how gradual switching to reproduction in annuals may arise from either stochasticity in growing-season length or design constraint (inability of small reproductive structures to absorb all photosynthetic products). He closed with a discussion of defensive allocation and the nuances of defenses against specialist vs. generalist herbivores. In the discussion, tillering ability in grasses was cited as optimal in a stochastic environment. Also, the explanation of optimality for woodiness in life forms was criticized as possibly including circular reasoning; an alternative explanation involving competition for light was offered.

Optimal acclimation of leaf photosynthetic capacity to light: finding appropriate constraints
Ülo Niinemets (Estonian University of Life Sciences)

Dr. Niinemets explained that mathematical optimization of canopy models allows one to calculate the nitrogen distributions within the canopy that should optimize whole canopy carbon gain. The nitrogen distributions predicted by these models, however, correlate poorly with actual measurements. Dr. Niinemets created a more realistic model of within-canopy profiles of foliage photosynthetic traits that included the cost of acclimation, protein turnover, and the time-scale of optimization. This resulted in better agreement between model predictions and data. In addition, acclimation time-constants were established through meta-analyses of light-transfer experiments. These acclimation times were so long that foliage photosynthesis is usually sub-optimally acclimated to environmental conditions, further underscoring the need to incorporate realistic constraints when constructing optimality models. The time scale of variability in light levels – hours, days, years – critically changes the optima. Dr. Niinemets also discussed constraints to within-leaf partitioning of N among chlorophyll for light absorption, Rubisco for CO2 assimilation, and electron transport capacity for reducing the product of assimilation. The optimal distribution is seen to depend on light levels. He made a model of responses to water stress that induces partial stomatal closure with alteration of photosynthetic dynamics. The model includes stages of stress perception, signal transduction, signal amplification, and response. The details in cell signaling are currently excessive. Signaling limitations in some species appear to constrain the approach to optimality, adding to the constraint from the cost of protein turnover. Yet another constraint derives from fundamental leaf structure; leaves with lignified cell walls may be unable to add cell layers to acclimate to higher light levels. More constraints are added by defensive allocation and by the need to shade competitors. The discussion period covered many more considerations that might be built into optimality models. These included the differential value of light early in the day vs. later in the day, the differences in functional tradeoffs in C4 and CAM plants vs. C3 plants, leaf orientation and clumping as acclimation mechanisms, and hydraulic architecture. The question was raised of how individual leaves undergoing acclimation sense the status of the rest of the tree. In response to a question about the best time step at which to resolve photosynthetic function, Dr. Niinemets offered some potential changes to the standard Farquhar-von Caemmerer-Berry enzymatic model of photosynthesis.

Group Discussion

The participants then held a group discussion with dual topics. First they discussed the important specifics of performing sensitivity analyses of their models. Several specific methods were mentioned as well as a method called FAST, using a library called sensitivity in the R statistical package. It was noted that different methods of sensitivity analysis are appropriate, depending on the speed of individual simulations, the number of parameters to be tested, and the prevalence of interactions among parameters. Regular spacing of parameter values may be suboptimal. Parameter correlations indicate that the model should be restructured. Discrete parameter values call for genetic algorithms or the like for sensitivity analyses. Analyses should incorporate Bayesian constraints that enforce rules of "no such combinations of parameters. Insensitivity to a given parameter or set of parameters indicates overparametrization. The occurrence of nonlinear switches can make sensitivity analyses into nightmares; these should be converted into semi-continuous differentiable parameters, or one should use the commercial package from ILOG. Next the participants discussed the development of shared database, and modeling platforms such as OpenAlea for FSPMs and grid computing. Much emphasis was placed on the practical implementation of model sharing, specifically making open source software available (to molecular biologists in particular), the instruction of potential users, and the documentation of code. The maintenance of a website in which the software runs on a server was presented as a less expensive alternative to open source software. However, in this scenario the user would be unable to inspect the code. Limitations to use of a modeling platform in common include the need for a development team that is stable for a long term, and the pitfalls of "stuffing everyone in the same room" as a limit on creativity. A perceived advantage of a common platform is the availability of large packages such as those for image analysis, which can only be developed by large teams. A need was cited for moving toward a Web-based service for the modeling platform. Another need is for feedback to developers as individual modules are being generated, before a stable product is obtained.

Optimal Control of Dynamical Biological System: Simplified Model of Balanced Growth and Development
Ilya Ioslovich (Faculty of Civil and Environmental Engineering, Technion)

Until recently, optimal control concepts have not been applied to the problem of greenhouse crop production because models of these systems are necessarily complex. Dr. Ioslovich developed a metamodel of reduced dimensionality, incorporating the vegetative, mixed, and reproductive stages, with the sink activity of the plant balanced with the available source supply of photosynthetic material. A time- and weather-invariant parameter, the 'optimal control intensity,' was determined analytically. The model was used with tomato plant data in order to demonstrate how one might increase greenhouse production efficiency. The model must account for partial fruit loss (abortion, etc.) and the loss of photosynthetic material as leaf structures are scavenged. Global optimization of control is assured by using the Krotov-Bellman sufficient conditions. The solution is nearly identical to that given using a much more complicated model, TOMGRO. In the discussion that followed, Dr. Ioslovich was asked how many variables constitute an excessive number for such optimization, to which he offered 4 or 5 as the answer.

Using models to enable integrative studies of rice morphogenesis regulation
Jean-Christophe Soulié (UPR AIVA, CIRAD)

Dr. Soulié followed with a pair of short talks. In the first talk, he described EcoMeristem, a structural-functional model used to simulate plant morphogenesis and study the physiology and genetics of phenotypic plasticity. Understanding the source(s) of this plasticity is important for breeding and management of rice and tropical grasses, which are increasingly grown in fluctuating environments prone to extreme temperatures, drought, and higher levels of carbon dioxide. EcoMeristem, which is currently limited to the vegetative phase, operates on a daily time step, using thermal time for process rates, and it tracks individual organs. It has been partially validated for two rice varieties. Plans are to adapt it to sugar cane and sorghum, as well as to move to the reproductive phase. The model can be executed simultaneously with Caribu in OpenAlea being used to model light interception. In the discussion of this model, it was noted that mechanistic approaches are lacking for some processes and that some of the regression models are weak. Also, the model might incorporate the effects of water stress on leaf appearance rates, while Dr. Soulie proposed that thermal time suffices.

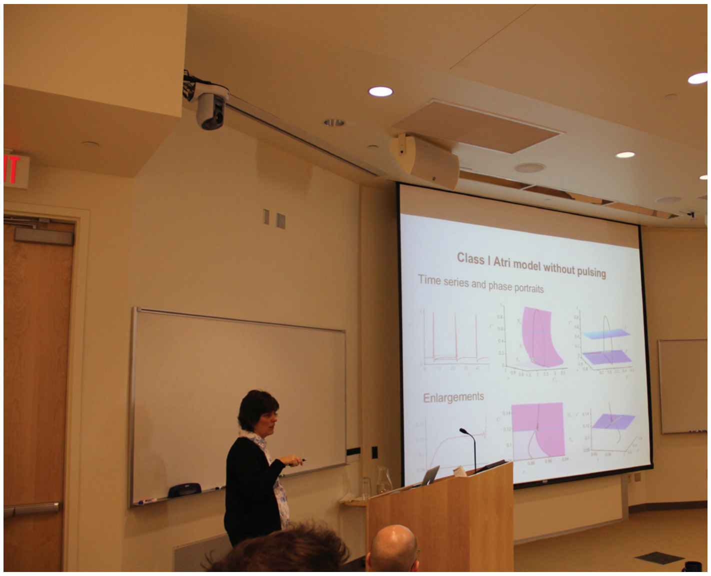
The second talk was a more general one on computational techniques, and detailed how Discrete Event System Specification (DEVS) can be used to couple different models together, each of which may be programmed in a different language. The user must provide an abstract simulator and specify the mathematical structure as input and output ports, models of internal states, state transition functions, and time advances. Models that are not in the style of DEVS can be out in a DEVS wrapper. DEVS has many extensions to incorporate difference equations, cellular automata, ODEs, Petri nets, etc.

Reformulating optimal impulse control problems as discrete optimal control problems
Rachel Leander (Mathematical Biosciences Institute)

Dr. Leander discussed how a certain class of impulse control problems, which arise frequently in biological control, could be reformulated as discrete optimal control problems. While many biological systems are modeled as systems of differential equations, human interventions (drug therapy, irrigation, etc.) are often as discrete events. The solutions can be solved by dynamic programming but they are difficult to obtain. Dr. Leander presented a discrete optimal control method that significantly simplifies numerical calculations. After outlining the method she worked through a specific example in which a fungus was controlled by the periodic application of fungicide. In the discussion period, it was offered that discrete time steps might offer simple solutions and that even linear control functions can generate bang-bang switching. The solution to the problem of scheduling fungicide applications (late in the season) appeared to be counterintuitive.

A Data Model of Root Gravitropism
Nathan D. Miller (University of Wisconsin)

Dr. Miller used data collected from 2000 time-lapse movies of Arabidopsis roots growing under controlled conditions, for three genotypes. The trajectories of the midline points in each movie were described by a tensor. Subsequent analysis by a method related to neural networks but perfectly invertible yielded two parameters that sufficed to describe growth of roots of different ages and genotypes in media of different mechanical properties. The first parameter described the growth rate (thus, the length of the growth zone) and tip angle, and the second described the differential growth along the top and bottom of the root that is achieved by some combination of the rates of cell division and cell elongation. In the discussion period, one topic was the minimum set of measurements needed, such that manual observations might suffice instead of expensive banks of cameras; there is no answer currently. Related to this was the question of whether or not the final image of the root, with some markers that were placed at selected times, could be inversely modeled to yield the two parameters without needing movies. Dr. Miller opined that this was not possible. Another question was how the gravitropic signals, which are generated at roots tips by statoliths, are propagated further back from the apex. It was also opined that the two growth parameters are not simply related to root age and seed size.



FRIDAY, OCTOBER 1
HOW DO WE ADVANCE?

From genes to patterns: mathematical models for plant development and evolution
Pablo Padilla (Institute for Applied Mathematics, University of Mexico)

Dr. Padilla discussed the gene regulatory network that controls the formation of floral organs (i.e. the differentiation of floral cells). Interestingly, the temporal pattern of floral organ formation is preserved across all 250,000 species of flowering plants. He reviewed key models that have been proposed. He and his collaborators then used data collected from empirical experiments to construct a gene regulatory network for floral cell differentiation. The network ultimately expanded to 15 genes with inhibition and activation, including self-activation for some genes. This network gave rise to a discrete dynamical system. The equilibrium states of the system correspond to cell types. Initially the equilibrium states did not correspond to the observed cell types. However, after three biologically plausible though hypothetical connections were added to the network, the updated dynamical system achieved the appropriate steady states. The gene network model was also used to predict the results of various genetic mutations. Biological experiments have since confirmed the models predictions, thus validating its structure. The discrete dynamical system was then converted to a continuous dynamical system, which was perturbed with noise so that the resulting Fokker-Plank equation could be analyzed. Starting from a biologically plausible initial state, this equation successfully predicted the temporal sequence of organ formation. Noise made the system robust, able to find the "wells" (4 final cell types) from any starting point, and the wells are bigger for the most critical organs, the stamens and carpels. The network also proved robust to elimination of single links, as expected biologically. In the discussion period, one note was that noise may be equivalent to deterministic changes in the environment, if the latter are sufficiently complex. Limit cycles are also possible in genetic networks, as in the circadian clock. Lastly, if the network is modified sufficiently, there may be a new set of stable states.

A brief review of progress and some remaining challenges in modeling plant development
Vince Gutschick (The Global Change Consulting Consortium, Inc.)

Dr. Gutschick focused on three ways that modelers can advance their art. Specifically he said that modelers could advance their art by sharing their tools (platforms, models, documentation, code quality checking), promoting their art through teaching and documentation of its value, and recognizing and adapting to the barriers that are imposed on them by scientific methods and nature. In the last category, he noted genetic complications (epigenetics, population genetic constraints, and loss of adaptive genetic variation) and the implicitness of tradeoffs in evolution and ecology. He reviewed the goals of six basic types of models: prediction of performance; inversion to obtain system descriptors; generating testable hypotheses; synthesizing knowledge; simplifying experimental design; and teaching biological principles. For each such type, he reviewed the goals, challenges, and some tools. For example, in forward modeling to predict performance, there is inherent potential for optimization. At the same time, there are challenges of complexity (with opposing pitfalls of overfitting and oversimplification), of developing useful statistical analyses, and of adequately testing model structure. Tools for advancing predictive modeling include sensitivity analyses, ensembles of simulations, and numerical adjoint equations. In inverse modeling, there are promising methods of delimiting parameter ranges. In generating hypotheses, a common default assumption is evolved optimality; failures indicate variously our lack of knowledge of selection pressures, real lags in adaptation, and constraints from phylogeny and population genetic structure. Dr. Gutschick ended with broad biological questions, including some that only modeling can answer, and other broad questions about the biological knowledge that we have and that we can build into models.

Group Discussion: How do we advance?

Participants then broke out into small groups to discuss how the plant modeling community might advance. A plenary discussion ended the workshop. One obstacle was the need to spread the capabilities in graphical user interfaces and visualization, within the community and to the experimentalists. Another was in the style of writing papers, with inadequate overlap between mathematical and biological emphases. We cannot afford to restart at the lowest levels. A suggestion was that a biologist might start research and then engage a mathematician to help formulate it; the problem would then be brought back to the community of mathematicians. Alternatively, some of us in the plant modeling community began with strong mathematical backgrounds and developed long-term relationships with strong biologists. Another suggestion was that people who study the process of learning could contribute to bridging the divide. It was noted that we generally do biology and recruit the necessary mathematics, not needing new mathematics. Extant mathematical techniques often serve well. Often it suffices to find isomorphisms between biological problems and mathematical formulations, such as between genetic network action and the Fokker-Planck equation. Finding students with strong biology and math backgrounds is imperative. Currently, students self-select, with those showing weakness in math then choosing biology, generating a fundamental bias in approach. Creating a dialog between mathematicians and biologists early on is required, and it will be both difficult and long in coming. One area needing redress is the teaching of biology, most commonly as fact-driven rather than hypothesis-driven. Also, we in the mathematical biology community have many beautiful models and simulations to share; we need to share them early in the education of students.

It was noted that fundamental differences in approaches are needed between addressing proximate mechanisms (gene action, e.g.) and addressing ultimate ecological and evolutionary questions. Many evolutionary biologists ignore proximate mechanisms, asking only if a mechanism could be the production of evolution. Some mathematical areas seem to have offered little to biology to date, despite initial promise, such as control theory and information theory. To advance biology, we must discard efforts to gather marginally useful data. We must also invent data sharing, such that experiments can be designed to give as much added value as possible. For example, if one is measuring leaf expansion, the added effort in measuring leaf N content may be small but may be very valuable to other researchers. Access to both data and models must be made facile, particularly using the Web effectively and with standard of quality assurance and documentation.

A critical need is to persuade funding bodies that modeling is important for the advance of biology. The group readily assented to taking on this task, first by generating a major opinion paper that we would call the Declaration of Columbus. Christine Beveridge will lead the effort, aided by all of us and by a number of people who were unable to attend the workshop. Our discussion notes should give us a good start on the paper. We need to disseminate this effort, pre- and post-writing, on the Web and directly to NSF and other agencies. This document should be a living document, like a wiki. A location that is widely apparent to biologists, mathematicians, and funding agencies must be sought. We should link to other institutions (MBI, ASPB) and regular meetings (FSPM).

Workshop 2: Circadian Clocks in Plants and Fungi

OCTOBER 25-29, 2010

Organizers: David Rand (University of Warwick), Daniel Forger (University of Michigan), Deborah Bell-Pedersen (Biology, Texas A&M)

Report written by Casey Diekman, Deena Schmidt, and Yunjiao Wang

OVERALL SUMMARY

Circadian (~24-hour) rhythms control the timing of many biological processes including leaf movements in plants and sporulation in fungi. Advances in understanding the biological mechanism of plant and fungal clocks have also helped inspire clock research in higher organisms. The goal of this workshop was to bring together theorists and experimentalists (some of whom are new to mathematical modeling or circadian rhythms) to better understand timekeeping in plants and fungi and how they relate to clocks in higher organisms, and also to foster interdisciplinary collaborations.

The workshop was organized around the following themes:

1. How do multiple feedback loops within the Neurospora and Arabidopsis clocks interact? How do individual feedback loops regulate circadian behavior?
2. How do circadian clocks keep a near constant period despite widely changing environmental conditions?
3. How can mathematical models be matched to time series data?
4. How do circadian rhythms synchronize to the external world and the circadian clocks of other cells?

MONDAY, OCTOBER 25

Genetic and Molecular Dissection of the Neurospora Circadian Oscillatory System: Genetics, Proteomics, and Epigenetics
Jay. C. Dunlap (Dartmouth Medical School)

Dunlap introduced the basic elements and dynamics of the Neurospora Crassa clock. The main component in the clock system is the protein FREQUENCY (FRQ). Two transcription factors, White Collar 1 (WC-1) and White Collar 2 (WC-2), regulate gene transcription of the frq gene. The newly produced frq mRNA then becomes translated into protein. Free FRQ protein quickly forms a complex with helicase FRH. Then the complex moves to the nucleus and phosphorylates WC-1 and WC-2, turning off transcription activity, and then moves back to cytoplasm. FRH gets phosphorylated and releases FRQ. At the same time, WC-2 is released from the promoter. Phosphorylated FRQ proteins are easily attracted to proteasome and get turned over. By this time, white collar transcription factors reappear on the promoter. This cycle repeats about every 22.5 hours. Dunlap pointed out that fungi and animals share the similar architecture in clock feedback loops, so the results in Neurospora are applicable to flies and humans. The experiments from his lab showed that rhythmicity can be observed at the molecular level. It was found that FRQ always occurs in the form of FRQ-FRH complex. FRH interacts poorly with White Collar transcription factors. His experimental results indicate that the act of promoting transcription destabilizes WC-1: as FRQ builds up, it promotes phosphorylation of WC-1, which inactivates it and thereby stabilizes it. Then he continued to discuss the activity of the FRH-FRQ complex. It was found that many clock functions are attributed to phosphorylation of FRQ, such as coordinating protein-protein interaction, setting the period length, and contributing to the mechanism behind temperature compensation. Lots of discussion occurred during this talk.

Circadian Control at the Post-Transcriptional Level: the Gonyaulax story
Woody Hastings (Harvard University)

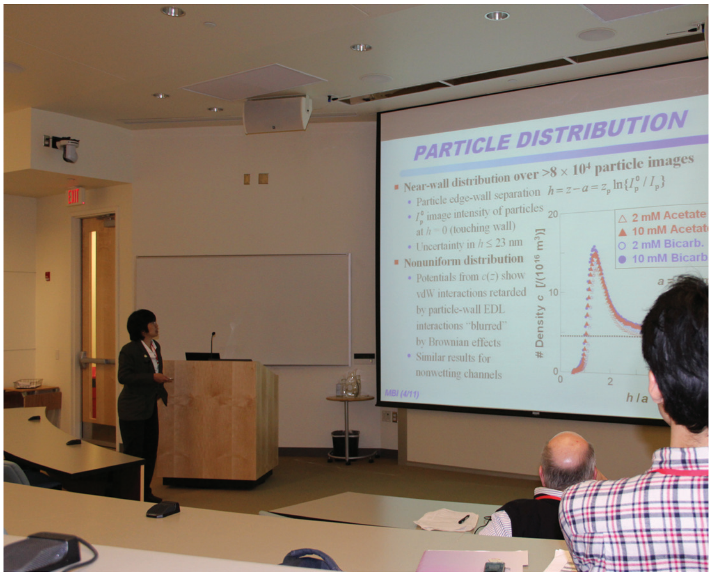
Gonyaulax is a large genus of phosphorescent marine dinoflagellates. Hastings discussed several results of Gonyaulax that have come out over the last half century: Translational control of circadian protein synthesis; Temperature compensation; Reversible loss of rhythms at a low temperature; Different rhythms may have different periods; Communication of circadian phase via the medium; Infradian and ultradian rhythms. Several different daily rhythms have been measured. A main question was: Is the daily rhythm observed due to the amount of luciferase or its regulation? It was found that both luciferin binding protein and luciferase are synthesized and destroyed every day. Synthesis of many proteins is circadian controlled, but not all proteins are circadian controlled. Temperature can influence circadian rhythms. Rhythms will be lost when the temperature is lower than 12 degrees Celsius, but can be restored after the low temperature. Hastings noted that only 1.5 degrees Celsius separates the permissive and non-permissive phases. In Gonyaulax, several different rhythms peak at different phases. Are they controlled by only a single mechanism at the molecular level? Moreover, different rhythms have characteristically different phase angle relationships, but these can be altered by conditions. Might circadian phase be affected by humoral factors? This is of continuing interest in the mammalian suprachiasmatic nucleus, where dozens of peptides have recently been reported; a unicell might be a favorable system to investigate the possibility. Also, do models for circadian systems have applicability to infra-ultradian rhythms? A circannual rhythm in Gonyaulax may be a good challenge for elucidating this mechanism. As in the first talk, there was quite a bit of discussion during Hastings talk.

Timekeeping in cells and timekeeping in networks
Daniel Forger and Richard Yamada (University of Michigan)

Forger talked about how different complex formations can influence dynamics. He presented a simple sequential model to address this issue: four proteins sequentially bind together, and then a final complex moves to the nucleus and regulates gene transcription. It forms a negative feedback loop. The simulation displayed different dynamics with different sequential order. Forger then discussed a more realistic model of the circadian system. He quoted Enright's paper and asked the question: if a population of cells exhibit rhythmicity, does every cell need be rhythmic? The answer is no. He showed some interesting synchronous phenomena observed in experiments and presented some numerical simulations. During the second half of the talk, Richard Yamada talked about sequestration as a possible mechanism for promoting oscillations. Negative feedback and delay promote oscillations, such as in the Goodwin model. What is the role of sequestration in time-keeping? It promotes the degradation of the activator-repressor complex. Yamada presented some details about numerical results for synchronization phenomena which were observed when cells were coupled via mean field methods, but each individual cell exhibited only damped oscillations. He showed that similar phenomena could happen in various other circumstances.

Multi-loop Structure in Plant Circadian Clock
Treenut Saithong (King Mongkut's University of Technology Thonburi)

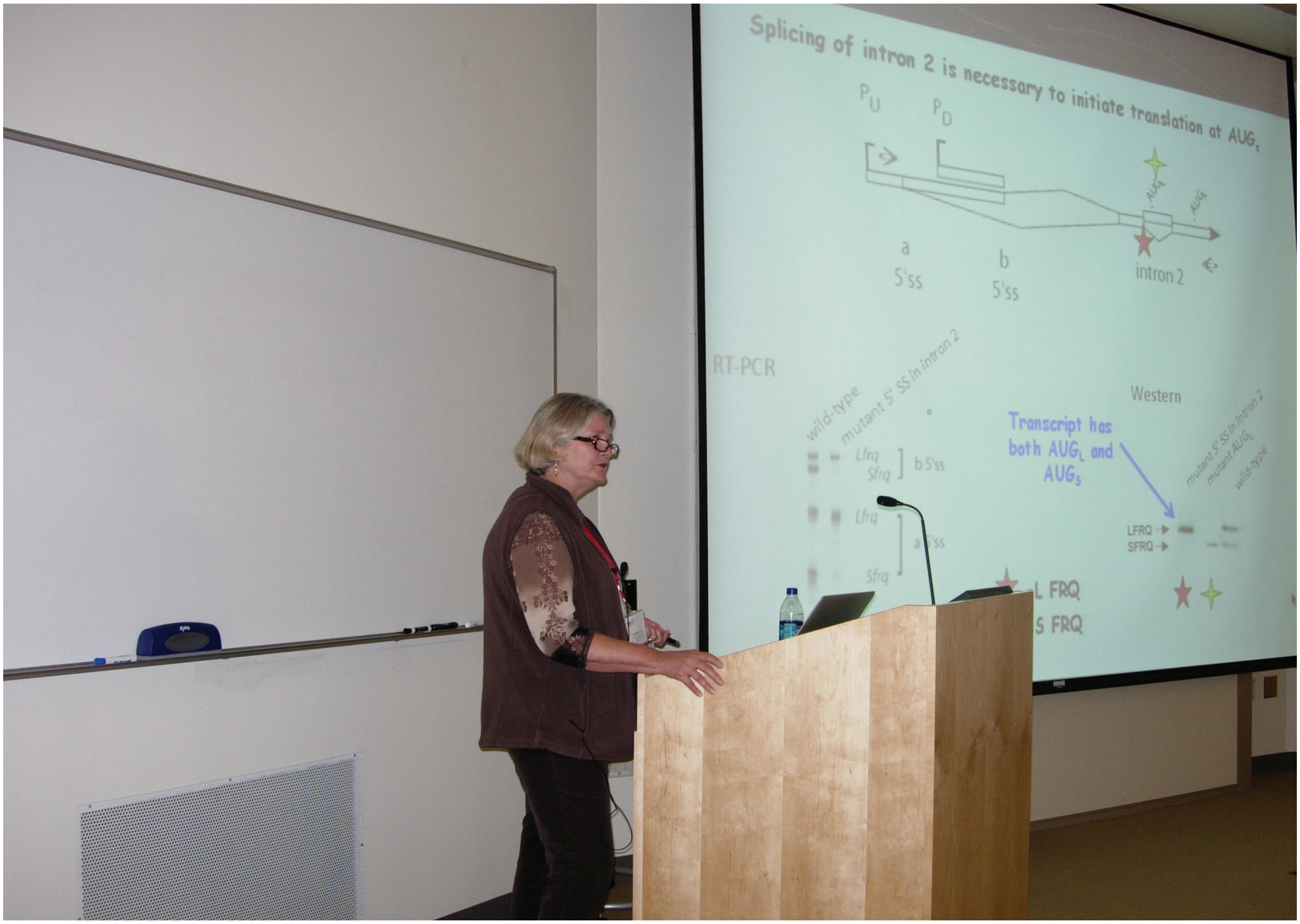
Saithong talked about the circadian clock in plants, specifically focusing on Arabidopsis. The circadian clock is a fundamental biological process of organisms ranging from unicellular to multi-cellular. Its network is believed to be formed from a group of genes and proteins connected in a negative feedback loop structure which generates a robust 24 hour-period oscillation. The molecular mechanism of the circadian clock has been studied across a range of organisms: fungi, insects, flies, mammals, and plants. Despite the apparently independent evolution of circadian clocks within these diverse organisms, certain characteristics are shared across all circadian clocks, including the ability to generate a 24 hour rhythm that is robust to the external/internal variations and can be entrained by rhythmic environmental signals (such as the light-dark cycle or temperature cycles). The first Arabidopsis clock model, denoted the 'one-loop' model, consists of a single negative feedback loop. Saithong talked about more complex models that have recently been published which suggest that two or three negative feedback loops are likely involved in the clock. She then discussed the effects of multiple loop structure and nonlinearity of the kinetics on model sensitivity and robustness. Robustness analysis can indicate both the relative plausibility of different models and also the critical components and processes controlling each model. Saithong concluded that multiple loops with interlocking structure and the degree of nonlinearity are therefore critical in contributing to the desired properties of a model as well as its capacity to match experimental data. Most of the work was done at the Institute of Molecular Plant Sciences and the Department of Biological Sciences at the University of Edinburgh.



TUESDAY, OCTOBER 26

How Fungi Keep Time: Circadian Oscillators and Rhythmic Outputs
Deborah Bell-Pedersen (Texas A&M University)

Bell-Pedersen talked about the circadian clock in Neurospora to explain how fungi keep time and how the clock regulates circadian output. About 20% of Neurospora genes are under control of the circadian clock system at the level of transcript accumulation, and the bulk of the clock-controlled mRNAs have peak accumulation in the late night to early morning. These data suggest the existence of global mechanisms for rhythmic control of gene expression. Signal control pathways involving MAPKs control many of the same genes that are regulated by the circadian clock. In particular, Bell-Pederson discussed the Neurospora OS pathway, a highly conserved phosphorelay signal transduction pathway that responds to changes in osmotic stress, and found that it functions as an output pathway from the main oscillator: Frequency (FRQ)/White Collar Complex (WCC), which is comprised of the products of white collar genes wc-1 and wc-2 as well as those of the frequency gene frq. Using ChIP/Solexa sequencing with known oscillator proteins, she showed that phosophorelay/MAPK pathway components are direct targets of the WCC and that they provide a direct connection between the clock and the output pathway. Activation of the OS pathway by the FRQ/WCC oscillator culminates in rhythmic OS-2 MAPK activity, which through time-of-day-specific activation of downstream



Jennifer Loros (York University)

effector molecules, controls rhythms in several target clock-controlled genes. Hijacking conserved signaling pathways by the circadian clock provides a new paradigm for global rhythmic control of target genes of the pathway.

Post-translational processes in the control of the Arabidopsis circadian clock

David Somers (The Ohio State University)

Somers gave the next talk which focused on the plant Arabidopsis circadian clock. Post-translational processes such as phosphorylation, SUMOylation and ubiquitylation control protein activity, localization, and turnover. Many core oscillator components of the circadian clock are nuclear localized but how the phase and rate of their entry contribute to clock function is unknown. TOC1, a pseudoresponse regulator (PRR) protein, is a central element in one of the feedback loops of the Arabidopsis clock. Both TOC1 and a closely related protein, PRR5, are nuclear localized, expressed in the same phase, and shorten period when deficient. Somers showed that TOC1-PRR5 oligomerization enhances TOC1 nuclear accumulation through increased nuclear import. Additionally, PRR5 recruits TOC1 to large subnuclear foci and promotes phosphorylation of the TOC1 N-terminus. His results demonstrate that nuclear TOC1 is essential for normal clock function and reveal a mechanism to enhance phase-specific TOC1 nuclear accumulation. Somers has also found that a second post-translational mechanism enhances ZTL protein stability through the activity of a ubiquitous chaperonin that plays a role in the clock different from animal systems. In collaboration with Janet Best, Tony Gallenstein, and Grant Oakley, the relationship between this new component, ZTL, and another stabilizer of ZTL (GIGANTEA) is being explored through a mathematical model that focuses on the importance of post-translational processes in regulating clock function.

Photo-Adaptation and Light Entrainment in Neurospora: VIVID Memories of Days Gone By

Michael Brunner (University of Heidelberg)

Brunner talked about light responses and photoadaptation in Neurospora. These processes depend on the photosensory light-oxygen-voltage (LOV) domains of the circadian transcription factor White Collar Complex (WCC) and its negative regulator Vivid (VVD). His group found that light triggers LOV-mediated dimerization of the WCC. The activated WCC induces expression of VVD, which then disrupts and inactivates the WCC homo-dimers by the competitive formation of WCC-VVD hetero-dimers, leading to photoadaptation. Interaction with VVD protects light-activated WCC from rapid degradation and thus allows a sizable fraction of WCC to equilibrate with the WCC dark form. In the photo-adapted state, VVD synthesis triggered by light-activated WCC is balanced by VVD-dependent inhibition of WCC. The VVD-mediated desensitization and stabilization of the light activated WCC explains on a molecular level how Neurospora can robustly entrain to artificial and natural photoperiods. During the day, expression levels of VVD correlate with light intensity, allowing photoadaptation over several orders of magnitude. At night, previously synthesized VVD serves as a molecular memory of the brightness of the preceding day and suppresses responses to light cues of lower intensity, such as moonlight. He concluded that VVD is essential to discriminate between day and night, even in naturally ambiguous photoperiods with moonlight. Brunner noted that this work was done in collaboration with Erik Malzahn, Stilianos Ciprianidis, Krisztina Kaldi, and Tobias Schafmeier.

Mathematical modeling of cell cycle and circadian rhythms as a coupled oscillator
Christian Hong (University of Cincinnati College of Medicine)

In most eukaryotic organisms, networks of cell cycle and circadian rhythms coexist and work coordinately to create optimal conditions for cells to grow and adapt to the surrounding environment. Cell cycle regulatory mechanisms include multiple checkpoints for controlled growth and cell divisions. The period of this oscillation, however, varies with external conditions such as nutrient and temperature. The cell cycle machinery is optimized for growth and division, but not for time keeping. Circadian rhythms keep track of time and provide temporal regulations in most eukaryotic organisms with a period of about 24 hours. In contrast to the period of the cell cycle, the period of circadian rhythms is relatively insensitive to external conditions such as nutrient and temperature. Cell cycle and circadian rhythms are coupled despite of their apparent disparate functions. The circadian gated cell division cycles are observed in various organisms from cyanobacteria to mammals. Yet, the implications of this coupling on the physiology of an organism are unknown. Hong used a mathematical model to study interactions between the cell cycle and the circadian clock and their implications in cell cycle regulations.

WEDNESDAY, OCTOBER 27

Temperature and the Neurospora Clock
Jennifer Loros (Dartmouth College)

Loros gave an impressive chronology of all the research she has been involved in regarding the effect of temperature on the Neurospora circadian clock. Temperature can affect rhythms in multiple ways, and the ability to maintain a constant period at different temperatures (temperature compensation, or TC) is considered a defining property of clocks. In 1986, Loros demonstrated the loss of TC the frq9 mutant. In 1997, Loros and colleagues showed that thermally regulated translational control of FRQ mediates aspects of temperature responses. In 1998, they investigated how temperature changes reset a circadian oscillator, and in 2003 found that the frq gene is required for temperature-dependent regulation of many clock-controlled genes in Neurospora. In 2005, two publications focused on the relationship between FRQ-protein stability and TC and temperature-modulated alternative splicing and promoter use in the frq gene. In 2008, a fully codon-optimized luciferase uncovered novel temperature characteristics of the Neurospora clock. And finally, in 2009, a role for casein kinase 2 in the mechanism underlying circadian TC was discovered. Also in 2009, quantitative proteomics revealed a dynamic interactome and phase-specific phosphorylation in the Neurospora circadian clock. This work demonstrated that phosphorylation of different FRQ residues can lead to changes in either period length or TC. The breadth of the research covered by Loros inspired an interesting discussion or whether the effect of other perturbations on the clock besides temperature (e.g. pH) should be cataloged in a comprehensive way as well. Extensive datasets on different perturbations in a variety of mutants, in tandem with mathematical models, could be used to tease out control coefficients for the components of the system.

Network changes in response to temperature driving a ROBuST circadian clock
Peter Gould (University of Liverpool)

Gould talked about his work in conjunction with the ROBuST project, a multi-institution collaboration tracing temperature effects through the Arabidopsis signaling network. ROBuST (Regulation of Biological Signaling by Temperature) focuses on interconnected light signaling, circadian, and cold acclimation pathways containing 56 components in total. To do this, ROBuST would like to use a high-throughput, universal-access assay. However, current technologies such as luciferase imaging, leaf movement, or CO2 assimilation, are either low-throughput or difficult to perform. Instead, Gould used a novel assay based on delayed fluorescence (DF), a recently identified output of the circadian clock, to screen 56 mutants of interest for circadian clock phenotypes in different light and temperature conditions. Based on the DF results, Gould concluded that buffering against temperature changes requires alteration of the circadian clock architecture in response to temperature. Gould also discussed additional work identifying new functions for several clock genes as regulators of temperature buffering. While DF data is high-throughput, it can be difficult to interpret and Gould said that better means of visualizing alterations in the circuit diagram are needed.

Homeostatic and Oscillatory Mechanisms in Plant and Fungal Nitrate Assimilation

Peter Ruoff (University of Stavanger)

Ruoff talked about how oxidative stress induced by nitrate and nitrate reductase (NR) is kept under control during day/night cycles. Robust, or perturbation-independent, homeostasis is often achieved through integral control. Ruoff sought to identify the molecular mechanisms that could lead to such control, and what determines the homeostatic set-point. For example, iron homeostasis in plants appears to be achieved by an outflow controller motif. In mammals, iron homeostasis is through an outflow controller in low iron concentrations but through an inflow controller in high iron concentrations. Ruoff then discussed oscillations in homeostatic controllers. Ruoff considered oscillatory nitrate assimilation in Neurospora, and looked at the relaxation kinetics to steady state using a luciferase reporter for transcriptional activity of the nit-3 gene. The conclusions from the experimental and modeling work were that nit-3 expression is oscillatory, and probably under circadian regulation, but there is still a need for experimental demonstration of the roles played by the nitrate/NR negative feedback loop. The talk spurred questions and discussions about whether or not it is surprising to see harmonic oscillations in a reaction-dynamics system, and the role of zero-order ultrasensitivity and Hamiltonian systems

Can mathematical analysis help uncover the design principles behind circadian rhythms?

David Rand (University of Warwick)

Rand began his talk by stating that clocks are not simple oscillators, and some of the functions they must perform seem conflicting at first glance. For example, they need to be able to entrain to environmental signals with the correct phase, but also be robust to (unimportant) fluctuating environmental variations. Rand's talk considered design principles for a clock. Most of Rand's talk fell under two theoretical concepts, the first being global sensitivity analysis. The idea here was that even if you have a high-dimensional model, with hundreds of parameters, the time series you get as a solution to the differential equations often lives in a flat ellipsoid and is effectively two-dimensional. This is because the effect of changing different parameters often does similar things to the solution, in other words their effects are highly correlated. Rand said that this is a fairly general result for highly-coupled systems, and the types of clock models the field is usually interested in, but would probably not be true for weakly coupled systems. Then Rand used the example of the Arabidopsis 3-loop clock model from Locke et al. to demonstrate how a system can buffer against fluctuations in an environmental variable. The Locke model already has light input built into it, and temperature dependence was added through Arrhenius relations. Using infinitesimal response curves and balance equations, Rand showed how the flexibility of clock networks allows them to simultaneously achieve evolutionary aims that are prima facae at odds with each other. Software tools for performing the type of analyses described by Rand are available at http://www.maths.warwick.ac.uk/ipcr/.

Amplitude/Temperature-Compensation: Data and Models

Stuart Brody (University of California, San Diego)

Brody gave the last talk of the day and focused on amplitude, a measurable but often neglected parameter of oscillators. Brody began by reviewing data on the Neurospora frq7 mutant, which has a period of about 30 hours, or 1.3X greater than wild-type (frq+). The frq7 mutant also showed weak resetting behavior (compared to frq+) when perturbed in various ways. Brody and colleagues proposed that these behaviors are due to an increase in amplitude for frq7, since an expansion of the limit cycle could lead to both a longer period and a clock that is less sensitive to resetting. This prediction was later verified by experiments measuring increased amplitude in frq7 vs. frq+. Brody then reviewed phase transition curves, and introduced the "reset zone" as a new way to measure the effectiveness of a pulse (Brody and Shaw, JBR, 15:225-240). The frq7 mutant has a larger reset zone than frq+, again due to an increase in size of the limit cycle. Brody then went on to discuss the relationship between amplitude and temperature, noting that an increase in temperature leads to an increase in amplitude (but not period) for circadian oscillators in many organisms. However, many non-circadian oscillators do not change their amplitude when temperature is raised. Brody proposed that the increase in amplitude is the mechanism of temperature compensation, i.e. the limit cycle expands in order to compensate for the increase in biochemical rates at higher temperatures and keep the period the same. This temperature-amplitude model can also make predictions about how the midpoint of an oscillator changes with temperature, a feature not found in other models. Brody concluded his talk by showing that is theoretically possible to convert a non-temperature-compensated to a temperature-compensated one. Brody's talk generated much discussion, from how amplitude of a clock is defined to how to reach a phase singularity experimentally.

THURSDAY, OCTOBER 28

Wavelet Analysis of Circadian Oscillations
Tanya Leise (Amherst College)

Leise's talk was aimed to give the audience a lecture on analyzing circadian oscillation data by using the wavelet method. She began with Fourier Analysis, focusing on the Discrete Fourier Transformation (DFT). Fourier analysis is a very powerful tool for analyzing signals that have time-independent wavelike features. However, because Fourier series consist of sines and cosines, which are periodic waves that continue forever, the method is not appropriate to analyze signals that have more localized features for which sines and cosines do not fit very well. Wavelet transformation is designed to model these types of signals. After introducing the wavelet method, Leise used several examples from real data to show how the method can be used. Many questions were asked from audience. We can see that the method has caught the attention of many system biologists.

Modeling the mammalian circadian clock: from single cells to cell populations
Didier Gonze (Universite Libre de Bruxelles)

From a dynamical point of view, the circadian clock is a self-sustained oscillator with period near 24 hours and robust to noise. The circadian clock controls many physiological processes and integrates multiple inputs. From a physical point of view, a circadian system is a complex system which consists of many pacemaker cells that interact with each other. An early model of the circadian clock in Drosophila was developed by Goldbeter in 1995, which consisted of five variables in a delayed negative feedback loop. Gonze introduced two more models including his three-variable model. One puzzling observation was that the periodicity decreases with the increasing of clock gene degradation. Further study has been done, but the question does not yet have an intuitive answer. Next Gonze introduced a newly developed model based on molecular information. The model contains 16 equations and has been used to study many physiological properties. Based on this model, Gonze and his collaborators found that the lack of phosphorylation will slow down the degradation. The model was able to connect many sleep disorder diseases with molecular structure and has identified that some sleep disorders are caused by lack of entrainment. Another question was how to use the model to suggest a method to restore synchronization. The phosphorylation rate is viewed as a critical parameter to restoration because of its relation to period. A paper by Barkar and Leibler (2000) suggested that the oscillation of the first model in 1995 is very sensitive to noise. Gonze and his collaborators developed another stochastic model and found that fewer molecules led to more noise. Then, based on a simplified model, they used a positive feedback loop to stabilize the system. He concluded that a positive feedback loop helps robustness of oscillations. Some interesting questions arose about the statement of a positive feedback loop promoting robustness. David Rand suggested that we need to give the reason why it could promote robustness, for example from an eigenvalue point of view. After the discussion, Gonze briefly introduced the dynamics of coupled pacemaker cells by mean field methods and discussed synchronization of clocks.

Understanding Conflicting Zeitgeber Experiments
Gisele A. Oda (Universidade de Sao Paulo, Brasil)

A Zetgeber is an environmental agent or event (as in the occurrence of light or dark) that provides the stimulus setting or resetting of an organism's biological clock. In order to assess the hierarchy in the entrainment of circadian rhythms, experimental studies might have altered the natural phase relationship between photic and non-photic zeitgebers. Oda presented numerical models and simulations to interpret the complex results that emerge from these conflicting zeitgeber protocols. She began with a symmetric two-node model to study the phase changing due to the interaction between two different agents. Then she altered the coupling nonsymmetrically to show possible influences due to the coexistence of two zetgeber protocols.

Molecular synchronization oscillators in vitro and in vivo: The example of the Kai system
David K. Lubensky (University of Michigan)

Lubensky discussed the circadian rhythm of cyanobacterium S. elognatus, illustrating that it can be reconstructed in vitro with only three purified proteins KaiA, KaiB, and KaiC. This is remarkable since people used to think that circadian clocks required negative transcriptional feedback loops. In order to understand the mechanism of the three element network, Lubensky and his collaborators constructed a network which consisted of two groups of nodes: five nodes representing states that favor phosphorylation and another five nodes representing states that do not favor phosphorylation. The reason for this is because there are many phosphorylation steps involved when the three elements interact. He went on to analyze the model and predicted how the amount of KaiA and KaiB influence the occurrence of oscillations by showing a bifurcation diagram. His prediction about the influence of KaiA and KaiB was recently confirmed by an experimental study. After the in vitro study of the sub-network, Lubensky posed the

Eva Farre (Michigan State University)

question: when the sub-network is embedded into the original circadian network, what is the role of this sub-network in the whole system? The KaiA-KaiB-KaiC post-translational network interacts with transcriptional feedback loops. His numerical study showed that the two coupled networks are better than just one network. Lubensky explained that the phosphorylation and transcription cycles combined together work over a range of growth rates without expensive degradation.

Global control of rhythmic gene expression by the transcription factor LHY
Siren Veflingstad (University of Warwick)

The work presented in Veflingstad's talk was based on a study of gene expression in the plant Arabidopsis. Numerous genes are expressed rhythmically: 10-20% of all Arabidopsis genes are controlled by the clock in LL, 80-90% of Arabidopsis genes can cycle in various conditions. The question is: how does the circadian clock regulate gene expression? The transcription factor LHY acts as part of the central components of the Arabidopsis circadian clock and is thought to regulate the expression of a wide range of output genes. The talk focused on the regulation role of LHY by using both experimental and computational methods. Veflingstad used Chip-Seq methods to identify target genes of LHY, looking for genome-wide binding sides. It was found that LHY binds with various strength and binding regions are not confined to the promoter regions. Over 5000 sequences were identified. GO analysis showed that LHY regulates many biological processes. The identified target genes exhibit a wide range of phases of expression, ranging from early morning to late night. Analysis of motif enrichment within LHY-binding regions identified several sequences. Computational analysis is still underway.

Characterizing a phase QTL gene in linkage group 6 of Neurospora crassa
Kwangwon Lee (Rutgers University)

Lee gave the last talk of the afternoon session. Lee introduced natural variation and QTL analysis, then discussed cloning of one major QTL gene. Traditional studies of genetic screenings of Neurospora are often carried out under unnatural conditions. Lee's experiments were done under a natural condition by simply (but cleverly) inverting the traditional method.

Many studies can be done with the new method. Quantitative Traits Loci (QTL) analysis allowed them to identify 43 additive QTLs for period and phase phenotypes in the three mapping populations. Thirty of the identified 43 QTLs (70%) were not linked to any previously characterized clock genes. Moreover, 27 QTLs (63%) were found to contribute to variation of phase (but not period). These results contradict the widely accepted view of phase, that phase is simply another expression of period in a cycling environment. Based on these results, they proposed that there are numerous uncharacterized genes that are involved in entrainment.

FRIDAY, OCTOBER 29

PRRs directly regulate the expression of output genes in Arabidopsis thaliana

Eva M. Farre (Michigan State University)

Farre presented data on the genome wide targets of pseudo response regulators (PRRs). In Arabidopsis, there are 5 circadian regulated PRRs that all peak at different times of day. The Farre lab's goal was to identify the targets of the clock components PRR7 and PRR9 through chromatin immunoprecipitation and DNA sequencing (ChIP-Seq). Confirmation of targets was then done through expression analysis. Up to 30% of genes in Arabidopsis are circadian regulated, but for most of these genes the mechanism for achieving a phase specific expression pattern is not known. Farre was able to show that PRR7 and PRR9 directly repress the expression of morning expressed output genes in Arabidopsis. Farre's talk led to a question about what can be done to follow-up on a region of DNA that ChIP-Seq has identified as interesting. Farre said a good approach would be yeast-one-hybrid in order to identify the cofactors that are actually binding the PRRs and the DNA. As for why there is such a big array of PRRs in plants, Farre and David Somers suggested it is to allow sequential activation and to repress the profile of CIRCADIAN CLOCK ASSOCIATED (CCA1) and LATE ELONGATED HYPOCOTYL (LHY) proteins to specific phases. Finally, it was also discussed that PRRs have light and temperature dependent phenotypes as well.

Mechanism and "modeling" of the Neurospora circadian clock

Yi Liu (University of Texas, Southwestern Medical Center)

The first part of Liu's talk was about the determination of circadian period length in Neurospora, which is controlled by FRQ phosphorylation and degradation. FRQ represses WCC activity and frq mRNA levels, forming a negative feedback loop. FRQ has more than 76 phosphorylation sites, and the majority of these sites exhibit rhythmic phosphorylation. Phosphorylation can either increase or decrease FRQ stability, and phosphorylation of WCs inhibits their binding to the frq promoter. Liu concluded the first part of his talk by presenting a model of WC activity consisting of two interlocked phosphate "counting" mechanisms. In the second part of his talk, Liu described experiments into the molecular mechanism of suppression of circadian rhythms in Neurospora by a crticial stimulus (Huang et al, EMBO 25:5349-5357). A resetting stimuli of proper strength applied at a critical time in a circadian cycle can lead to arrythmicity. This is known as a phase singularity, a point at which phase is ambiguous and near which phase takes on all values. Liu's group found they could drive wild type and mutant Neurospora strains to the singular point by a shift in temperature. They found that after the singularity behavior, there was a random distribution of phases. Their results led them a model of singularity behavior as a 2-step process: first, a critical stimulus abolishes rhythms in individual cells, after which biological noise restarts the oscillations but the population is now desynchronized. Liu's talk prompted a discussion of the spatial distribution of phase, considering the tendency of Neuroposra and other fungal cells to form hyphae (multiple cells surrounded by a tubular cell wall).

Circadian gating of cell divisions revealed in single cyanobacterial cells

Qiong Yang (Stanford University)

Yang began her talk by highlighting the many orders of magnitude spanned by the periods of biological rhythms, from neural spike trains (less than a second) to rhythms in ecology and epidemiology (years). Yang considered how two essential rhythmic events, circadian rhythms and the cell cycle, coordinate their oscillations in the cyanobacterium Synechococcus elongates. Cell division events and circadian phase were tracked simultaneously in single cells. The data confirmed interesting phenomena of synchronization predicted by a simple modeling framework, and suggested that the circadian clock "gates" cell division. The gating function which best fit the data shows that cell cycle progression slows during the night but is uniform across cell cycle phases. Since the modeling approach used here was quite general, it can be readily applied to quantify the interactions between other coupled oscillators.

Discussion Sessions

Throughout the week, there were several sessions dedicated to interactive discussions between experimentalists and theorists. To facilitate these sessions, if there were any terms or concepts introduced during the workshop talks that people felt needed further clarification or warranted more conversation, they would add it to a list on the whiteboard in the front of the auditorium. During the discussion sessions, we would go through the list and have a dialogue on each term or concept. Some of the topics covered included: clocks versus oscillators, master versus slave oscillators, the gamma distribution, masking, entrainment, the "black widow" hypothesis, the Arnold mapping system, hysteresis, and models of photoadaptation. These discussions were very fruitful for bridging the gap between "wet" and "dry" science.

Workshop 3: Ecology and Control of Invasive Species, Including Insects

FEBRUARY 21-25, 2011

Organizers: Mark Lewis (University of Alberta), Ottar Bjornstadt (Penn State), Subhash Lele (University of Alberta), and Sergei Petrovskii (University of Leicester)

Report written by Juan Gutierrez, Suzanne Robertson, and Dan Siegel-Gaskins

MONDAY, FEBRUARY 21

Spatiotemporal Dynamics Behind Invasions In Cyclic Populations
Jonathan Sherratt (Heriot-Watt University, Edinburgh, UK)

Dr. Sherratt stressed the fact that many invasions occur as a result of climate change, and offered examples of predator-prey invasions in situations where predator-prey interactions drive population cycles. Dr. Sherratt explored wavetrain solutions in populations with cyclic dynamics and presented several numerical examples of periodic spatiotemporal oscillations, spatiotemporal chaos, and a state in between. He also discussed how to determine which of the behaviors will occur, as a function of ecological parameters. The characteristic invasion profile is a band of regular oscillations immediately behind the invasion front, which undergoes a subsequent transition to chaos. Dr. Sherratt explained that as a result of this, the question of "When is a wavetrain stable?" has evolved to researching "When is the wavetrain bandwidth smaller than the habitat?"

Patchy Invasion: Exotic Spread of Exotic Species or a Paradigm Shift?
Sergei Petrovskii (University of Leicester)

Dr. Petrovskii started his talk by defining three stages of biological invasion: introduction, establishment, and geographical spread. Each of the stages has its own specific mechanisms and implications, which require application of specific research approaches. Then, the talk focused on the challenges arising during the stage of the geographical spread and the factors that affect it: heterogeneity of the environment, human assisted dispersal (a.k.a. stratified diffusion), predation, impact of pathogens, etc. A well-developed theory based on diffusion-reaction equations predicts a simple pattern of alien species spread consisting of a continuous traveling boundary or 'population front' separating the invaded and non-invaded regions. Dr. Petrovskii explained that the 'population front' theory derived from diffusion-reaction theories is at odds with some observations, since in some cases the spread takes place through formation of a patchy spatial structure without any continuous boundary. An example of this is gypsy moth spread in the USA. He emphasized that the importance of the stratified diffusion may be significantly overestimated, and that the patchy spread is, in fact, due to predation or an infectious disease and its growth is damped by the strong Allee effect. The patchy spread described by a diffusion-reaction model appears to be a scenario of alien species invasion "at the edge of extinction" and this can have important implications for the management and control of the invasive species. He showed that patchy spread is not an exclusive property of the diffusion-reaction systems but can be observed as well in a completely different type of model such as a coupled map

lattice which is capable of taking into account environmental heterogeneity. Finally, Dr. Petrovskii argued that these theoretical results taken together with the evidence from field data may result in a paradigm shift: A typical pattern of exotic species spread is a patchy invasion rather than the continuous population front propagation.

The effect of disease on invasions

Frank Hilker (University of Bath)

Dr. Hilker's talk addressed the issue of variation in the success rate of exotic species after they are introduced into a new environment, specifically how some invasive species are able to establish themselves and thrive, while other populations cannot persist. One existing theory, the enemy escape hypothesis, suggests some species flourish in the absence of natural enemies present in their native habitat, such as infectious disease. Dr. Hilker considers the possibility of disease following an invading host in the wake of the invasion. He shows that if the pathogen catches up to the host it can slow down, halt, and even reverse the invasion front, resulting in sudden "invasion crashes." Dr. Hilker concluded his talk by discussing the implications of his results for the biological control of invasive species. Using disease as a bio-control agent can lower population levels of an invasive species, but may not be enough to eradicate the pest. In addition, one must use caution when combining controls, as using this method in conjunction with other forms of control such as culling may be less effective than expected or even counteract the original form of control.

Beyond arrival: Inferring competition-environmental interactions that allow establishment

Jim Clark (Duke University)

After arrival, an invading species must be able to develop a niche in its new environment in order to thrive. Dr. Clark's talk addressed how to predict when invaders will successfully become established, considering both competitive interactions with resident species as well as environmental variation. He emphasizes the need to consider competitive and environmental interactions on an individual scale, rather than the species level, as responses may differ depending on what other conditions individuals are exposed to. Individuals may respond more to a certain input (i.e. light, moisture, temperature) when a second input is either low (negative interaction, or "buffering") or high (positive interaction, or "amplification"), and these interactions are often unknown. Dr. Clark looks at how interactions of different types of inputs control the niche space, defining the environment in which we can expect an invader to be able to thrive. Niche models look at correlation in space between species abundance and climate variables, but don't get at the individual scale where interactions of interest are occurring. Dr. Clark analyzes large spatio-temporal observational and experimental data sets for tree species (both residents and invaders) in order to gain information about the most competitive and environmental interactions on the individual level, focusing on the sign of the most important interactions. He concludes his talk by discussing applications to the invaders Ailanthus altissima, hemlock and dogwood.

TUESDAY, FEBRUARY 22, 2011

Invasion speeds and sensitivity analysis in variable environments
Hal Caswell (Woods Hole Oceanographic Institution)

Dr. Caswell first reviewed how to calculate the speed of an invasion from stage-structured integrodifference equation matrix models. He then showed how to extend those results to environments varying in time. He considered both periodically (alternating "good" and "bad" years) and stochastically varying environments, where temporally varying parameters could be related to demography (i.e. fertility), dispersal, or both. Dr. Caswell also looked at how changes in these parameters affect invasion speed, noting this sensitivity analysis could be useful for comparing management strategies. He ended his talk by discussing the types of data needed to calculate invasion speeds for real biological systems. At the minimum, one would need demographic data and dispersal data, along with a model for the environment.

Suzanne Lenhart (University of Tennessee, Knoxville)

Applying wavespeed models to real-world issues: conservation, climate change and invasions
James Bullock (Centre for Ecology & Hydrology)

Dr. Bullock's focus was on the application of wavespeed models to ecological problems including plant re-introductions (such as the yellow rattle Rhinanthus minor), the ability of species to shift their ranges with climate change (determining best and worst case scenarios), and the control of invasive species (such as Rhododendron ponticum). Wavespeed models can give significant insight into these topics even though they are biologically much simpler than complex simulation models. Dr. Bullock also discussed the ability to incorporate dispersal data into wavespeed models, both for measured dispersal data as well as dispersal kernels derived from mechanistic models.

Management of spatial populations
Alan Hastings (University of California, Davis)

Dr. Hastings began by discussing the problem of Spartina alterniflora invasion in the western United States. Spartina is a perennial deciduous grass native to intertidal wetlands in the eastern United States that is replacing native species in the San Francisco Bay and the Willapa Bay of Washington state, resulting in reduced biodiversity and significantly-altered environments. In designing strategies for the optimal control of Spartina, Dr. Hastings used a spatially-explicit stochastic simulation and showed that a weak Allee effect slows invasion. He then used his modeling to address the following control questions: (1) how much Spartina needs to be removed every year to eradicate invasion within 10 years, and (2) is it best to prioritize removal of fast-growing but low seed producing clones, or is better to prioritize removal of slow-growing but high seed producing meadows? The objectives are to eradicate Spartina invasion within 10 years, and also to minimize the product of the removal cost and the risk of colonizing other sites. Dr. Hastings concluded, among other things, that the optimal approach is a time-dependent one, and there is a cost associated with waiting to act on Spartina removal. Clearly, models such as those described in the talk can play a key role in invasive species management, for example, by pointing out the information required to make informed decisions.

Optimal control applied to models of invasive population dynamics
Suzanne Lenhart (University of Tennessee, Knoxville)

Dr. Lenhart began her talk with some background on the subject of optimal control theory, a subject dating back to 1950 with the developmental work done by Pontryagin and collaborators. She followed with three examples of the use of optimal control as a tool to find intervention strategies in models of invasive species. The first example was one attributed to Moody and Mack (1988), who considered a finite number of satellites with a main focus and allowed either all satellites to be removed or an equivalent amount of the main focus to be removed. As a simple extension to this work, Dr. Lenhart allowed for more than one control action and a finite time horizon, with the goal of minimizing the amount of area covered by the invasive species and the control cost. In this extended case it was found that applying some control to central focus and some to satellites was in fact the optimal solution. A second example given by Dr. Lenhart was a native-invasive problem, specifically, the invasion of salt cedars into territory populated by cottonwood trees. In this case, the control variable is the amount of river flooding, as the cottonwoods rely on natural flooding and the salt cedars are more drought-resistant. Using this example Dr. Lenhart was able to obtain novel existence results of optimal controls for certain growth function structures. A third example of the use of optimal control in invasive species modeling was one that employed integro-difference equations, which possess many of the attributes of continuous-time reaction diffusion equations and arise naturally in population biology.

MBI Postdoc Juan Gutierrez presents his multimedia poster.

WEDNESDAY, FEBRUARY 23, 2011

Confronting perfect models with imperfect data using data cloning
Subhash R. Lele (University of Alberta)

Dr. Lele explained the divergence between continuous differential models and data acquired in discrete time and discrete space. Hierarchical models are a convenient way to model such imperfectly and partially observed processes. Dr. Lele discussed estimability issues that arise when the complexity of the model exceeds the complexity of the data, and presented a simple computational method that exploits advances in Bayesian computation, in particular the Markov Chain Monte Carlo method, to conduct statistical inference for hierarchical models. This includes (i) parameter estimation, (ii) confidence intervals, (iii) model selection, and (iv) forecasting future states and the uncertainty associated with such forecasts. Such method provides a simple graphical test to check if the full set of parameters is estimable, and whether a specified function of the parameters is estimable. Dr. Lele illustrated data cloning in 1) Population Viability Analysis in the presence of measurement error, 2) Two species Leslie-Gower Competition model, and 3) Analysis of systems of differential equations arising in epidemiology and ecology.

Stochastic logistic model with environmental noise
Brian Dennis (University of Idaho)

Dr. Dennis presented the origins of the logistic equation, and described how ecologists have handled the statistics of fitting the logistic model in a variety of ad hoc ways. Ecology textbooks are largely silent about estimating the unknown quantities in the logistic. In fact, field data departs from the model in several ways that would lead by statistical principles to different statistical methods for estimating parameters and predicting future outcomes. Dr. Dennis introduced a stochastic version of the logistic model that corresponds to a diffusion process with environmental-type noise. The equilibrium (carrying capacity) resulted in a gamma probability distribution, with many statistical properties being directly derived from the model. Dr. Dennis presented calculations based on singular perturbation, for the full transition probability distribution of the process. The approximation turned out to be accurate for fitting the model to time series data. The model proved to have the convenient property that the time intervals between observations could be unequal. Dr. Dennis presented various examples that used the model for statistical analysis of population time series.

Predation, competition and infection in a noisy environment
Horst Malchow (University of Osnabruck)

Dr. Malchow started by introducing the problem of modeling spatiotemporal pattern formation in plankton populations, driven by fish and virus (lysogenic and lytic cycles). These interactions give rise to the stud of infection of prey and/or predator and epidemic spread mediated by the variability of the environment, chaos, and random processes. Biological invasions including the spread of infectious diseases have strong ecological and economical impacts. Dr. Malchow presented Holling-type II and III predation as well as Lotka-Volterra competition models with possible infection of the prey or one of the competitors. The interplay of local predation, intra- and interspecific competition as well as infection and diffusive spread of the populations were suggested as causes for spatial and spatiotemporal pattern formation. The environmental noise may have constructive as well as destructive effects. In regards to competitive invasion of a variable environment, a plant competition model was considered for conditions of invasibility of a certain model area occupied by a native species. Short-distance invasion was assumed as diffusion whereas long-distance seed dispersal was assumed stratified diffusive or advective. The variability of the environment due to contingent landslides and artificial causes such as deforestation or weed control leads to the temporary extinction of one or both species at a randomly chosen time and spatial range. The spatiotemporal dimension of these extreme fragmentation events as well as a possible selected harvesting or infection of the invading weed turn out to be the crucial driving forces of the system dynamics.

THURSDAY, FEBRUARY 24, 2011

Two-Sex Invasions: The Effects of Sex-Biased Dispersal on Invasion Speed
Michael Neubert (Woods Hole Oceanographic Institution)

Dr. Neubert constructed a two-sex integrodifference equation model that overcomes limitations of more common one-sex dynamical models, most notably their inability to account for sex-related biases in dispersal and mating behavior. He then used this model to derive an explicit formula for invasion speed. A result of this work is that sex-biased dispersal may have a significant effect on invasion speed by skewing the operational sex ratio at the invasion's low-density leading edge. The precise nature of this effect on invasion speed depends on complex interactions among the direction of dispersal bias, the magnitude of bias, and the relative contributions of females and males to local population growth.

At the end of his talk, Dr. Neubert turned the microphone over to Tom Miller (Department of Ecology and Evolutionary Biology, Rice University), who detailed some related experimental work. Dr. Miller used a bean-eating beetle, Callosobruchus maculatus, as a laboratory model system to determine if the effects of sex-biased dispersal can be seen in a real biological invasion. He found that the experimental results are consistent with quantitative predictions of two-sex invasion theory, but that the experiments also suggest new challenges in accounting for non-stationary dispersal distributions.

Integrodifference equations for invasive species - some recent developments
Frithjof Lutscher (University of Ottawa)

Integrodifference equations have played an important role in the field of ecology, providing a very natural and general framework for modeling the spread of certain invasive species, specifically those that have distinct growth and dispersal phases during their life cycles. Many insect species satisfy this description, in particular where climate imposes strong seasonality. Dr. Lutscher began with a brief introduction to integrodifference equations and explained several common approximations that can be used to identify important spatial scales and simplify model parameterization. In particular, the so-called "kurtosis approximation" can be used to give an upper-bound on invasion speed, and the "average dispersal success" approximation can be used to develop estimates of critical reserve size for systems comprising single patches or simple metapopulations. He also detailed how the results differ when an Allee effect is included, and concluded with some open and challenging questions for integrodifference equations as applied to density-dependent dispersal of invasive species.

Effects of endogenous versus exogenous sources of spatial heterogeneity on population stability and persistence
Karen Abbott (Iowa State University)

The first half of Dr. Abbott's talk dealt with exogenous variability (variation in the environment, such as patchy resources) and its role in the spread of the invasive seaweed Sargassum muticum. Sargassum establishment success increases with the amount of available bare rock on which it can settle. Benthic grazers such as mollusks and sea urchins can clear rock; mollusk disturbances give rise to many small patches of bare rock, while sea urchins clear fewer but larger areas of rock. Dr. Abbott built an integrodifference equation model for Sargassum spread, her results revealing the importance of the spatial distribution of exogenous variation. She found mollusk disturbances alone are enough to allow Sargassum to invade, while sea urchin disturbances will only help the invasion if they are very large and numerous. The second half of Dr. Abbott's talk focused on the effects of dispersal in metapopulations, now considering endogenous heterogeneity (variation either in the distribution of the invading species itself or due to direct interaction with the invading species). Dispersal among subpopulations can lead to dispersal-induced temporal stability as well as spatial synchrony, two phenomena that have opposing effects on extinction risk. Dr. Abbott explores the relationship between dispersal and synchrony in order to understand their combined spatiotemporal effect on a population. She finds a positive relationship between stability and synchrony, rather than the negative relationship suggested by previous work. She concludes that dispersal can have a positive effect on both synchrony and enhanced stability, as long as there is some asynchrony remaining in the population.

Reproductive Asynchrony, Allee Effects, and the Maintenance of a Geographic Range Boundary for a Pest Insect
Bill Fagan (University of Maryland, College Park)

Dr. Fagan's talk focused on the issue of how far, rather than how fast, a species will spread. He presented a case study of the evergreen bagworm, Thyridopteryx ephemeraeformis. This tree pest species has a very well defined limit to its midwestern geographical range, despite the continued availability of hosts outside this range. The life cycle of the bagworm suggests reproductive asynchrony and phenology are important concerns for this species. Females have a lifespan of less than 14 days, spent entirely within their bag, and males have an adult lifespan of only 2 days in which to find a mate. Dr. Fagan presented data showing that the fecundity and survivorship of both eggs and pupae decline with increasing latitude, reaching nearly 0% at the northern boundary of the species' range. There is also an associated decline in population numbers and increase in extinction risk with increasing latitude. Dr. Fagan used a system of nonautonomous differential equations to model bagworm populations and explore the role of factors such as reproductive asynchrony and climate in generating the Allee effect associated with determining the edge of this species' geographic range.

FRIDAY, FEBRUARY 25, 2011

Marine bioinvasion in the network of global shipping connections
Bernd Blasius (University of Oldenburg)

As a motivating example, Dr. Blasius detailed how the bubonic plague spread across Europe. Although on a very large scale it appears that the movement of the plague took the form of a spreading wave, on closer inspection it is clear that the plague was first brought to Europe by the sea trade, and the cities with large sea ports were the ones initially affected and which served as a number of plague foci. Thus, transportation networks play a significant role in the study of invasion patterns. In fact, with 90% of world trade carried by sea, global shipping constitutes the world's largest transportation vector for marine bioinvasion, accidentally transferring numerous species around the world. Dr. Blasius used information about the itineraries of 16,363 cargo ships during the year 2007 to construct a network of shipping connections between ports. The resulting network possesses a heavy-tailed distribution for the connectivity of ports with systematic differences between ship types (e.g., container ships vs. bulk dry carriers). By coupling the shipping network with biogeography and environmental conditions at the ports, Dr. Blasius was able to quantify the likelihood of invasion by the exchange of ballast water. The model also allowed for the identification of high risk invasion routes, hot spots of bioinvasion, and major source regions from which bioinvasion is likely to occur. The model predictions were compared to and in agreement with data taken from various locations in the world. Despite its simplicity, Dr. Blasius' data-driven model exhibits complex dynamics and shows many properties that set it apart from similar models of epidemic spread or cascading failures on complex networks.

Models and Data for Invasive Spread Across Lake Networks
Mark Lewis (University of Alberta)

The model organism that was the focus of the talk is the spiny waterflea, Bythotrephes longimanus. This invasive species is spread by recreational boaters moving between the 500 interconnected lakes in the Canadian shield, and by modifying invaded lake trophic structure has a major ecological impact. In particular, the waterflea outcompetes native zooplankton, with an impact magnitude estimated to be similar to that of acid rain. Among the goals of Dr. Lewis' work are predicting the likelihood of given lake being invaded and understanding the processes that drive lake invasion. He used a stochastic gravity model, parameterized by boater survey data, in which the number of trips linking lakes is a random variable with a magnitude that is a nonlinear function of empirically measured quantities such as lake size and distance between lakes. As it turns out, Dr. Lewis' 'gravity score' is the single best predictor of invasion, with lake chemistry being less important. He also developed an establishment model that estimates the probability that an invasive population will establish at a given lake, depending upon local physical and chemical conditions. The hybrid gravity/establishment modeling approach proved to be very effective at determining which lakes become invaded as the invasion spreads across the complex network.

Workshop 4: Insect Self-organization and Swarming

MARCH 14-18, 2011

Organizers: David Sumpter (Uppsala University), Madeleine Beekman (University of Sydney), Stephen Pratt (Arizona State University), Vijay Kumar (University of Pennsylvania), Chad Topaz (Macalester College)

Report written by Rachel Leander, Yunjiao Wang, and Kun Zhao

MONDAY, MARCH 14, 2011

Moving in the crowd: Ants hold the key to traffic chaos
Audrey Dussutour (DYNACTOM, CRCA)

The first talk discussed recent experimental studies of ant traffic that give deep insight into the mechanisms of traffic organization and regulation. In particular, these studies indicated that ant colonies are self-organized, adaptive, and highly flexible. By comparing ant traffic flows on wide and narrow bridges, it was concluded that flow of unburdened ants is higher on wide bridges, while flow of food-laden ants is higher on narrow bridges. Furthermore, traffic flow on the narrow bridge exhibited temporal organization, while traffic flow on the wide bridge exhibited spatial organization. Both patterns of organization enhance information transfer, and result from individual based rules that depend on the ant's status and direction of travel. Specifically, burdened and outbound ants are given the right of way. A cover was then placed on the bridge in order to constrain the size of food particles that the ants could carry. At the individual level, the ants responded by altering the shape and size of their leaf fragments. At the collective level, however, the total traffic pattern remained the same. The ants compensated for the reduction in leaf fragment size by bringing more fragments to the nest. In fact, the rate of food return, estimated from both fragment size and the number of fragments delivered per unit time, was higher in presence than in absence of the height constraint.

Moving in the crowd: Ants hold the key to traffic chaos
Jean-Louis Deneubourg (Libre de Bruxelles)

Dr. Deneubourg talked about aggregation in multi-patch systems. He used modelling to show that in heterogeneous environments social behaviours in conjunction with environmental preferences generate a diversity of collective patterns/responses. The model was characterized by seven parameters that determined individual behaviour and environmental characteristics. Model simulations showed that when individual behaviour is fixed, environmental variation could produce diverse patterns of aggregation, including segregation. Furthermore, when individual behaviour is modulated by social interactions, collective discrimination and collective memory are generated. It was also observed that different phenomena obey the same network of positive/negative feedbacks with the same collective responses.

Self-organization in insect societies: past, present and future
Nigel R. Franks (University of Bristol)

The application of self-organization theory to social insect studies has been remarkably successful. Despite, or rather because the models that result are provocative, naive, and oversimplified, they motivate experiments that challenge misconceptions and foster progress. The interplay between reality and representation exposes errors and misunderstandings, and insect studies have gained great momentum from the natural, yet uneasy, tension between mathematical and empirical explanations. But most of all, this interdisciplinary collaboration has been a success because mathematicians and scientists have worked in tandem to design both models and experiments. Dr. Franks illustrated these points with examples. He then outlined future directions in which research of self-organization studies may proceed.

Division of labor and emergent adaptation
Paulien Hogeweg (Utrecht University)

Dr. Hogeweg reviewed some of the questions and hypotheses that led researchers to apply agent based modelling to the study of emergent behaviour within insect societies. She then discussed some more recent work on the evolution of the division of labor and provided insights into how these models might impact our understanding of insect societies. Specifically, these models have showed that spatial systems with local interactions can prevent evolutionary collapse of cooperative replicating systems, at the level of viability, which means that they represent an evolutionary stable strategy. This is because the division of labor prevents the collapse of these systems.

Parallel work and parallel play
Fred Adler (University of Utah)

Dr. Adler began by describing the development of social play in humans. In human children, parallel play describes two or more children playing side by side, perhaps using the same toy but for different purposes, and only occasionally modifying their behavior in response to the other. It forms an early stage of social development, following solitary play and generally preceding social and cooperative play. Dr. Adler used mathematical models of long-term interactions between ant colonies in order to analyze the dear-enemy effect and classify social work in ant colonies. Dr. Adler and his collaborators showed that ant colonies could make robust context dependent decisions with only limited information sharing.

TUESDAY MARCH 15, 2011

Modelling flocks and swarms
Leah Edelstein-Keshet (University of British Columbia)

Dr. Keshet reported some work on the link between individual behavior and the dynamics of the swarm. Simulation studies displaying life-like swarm behaviour lack rigorous comparison with actual data because our ability to collect field data of sufficient quality is limited. Recently, Dr. Keshet bridged this gap by gathering and analysing a high-quality dataset of flocking surf scoters, forming well-spaced groups of hundreds of individuals on the water surface. By reconstructing each individual's position, velocity, and trajectory, the spatial and angular neighbour-distribution plots were constructed, revealing a distinct concentric structure in positioning, a preference for neighbours directly in front, and strong alignment with neighbours on each side. Data were fit to zonal interaction models and individual interaction forces were sufficient to generate the observed macroscopic spatial patterns. Specifically, strong short-range repulsion, intermediate-range alignment, and long-range attraction, as well as a weak but significant frontal-sector interaction with one neighbour were sufficient to generate the observed macroscopic patterns.

From swarms to cannibalism to obesity: lessons from locusts
Stephen J. Simpson (The University of Sydney)

Dr. Simpson began by discussing behavioural changes in locusts. Specifically, stimulation of touch-sensitive hairs on the back legs of the locust causes a rapid shift in behavior, changing shy reclusive green locusts into brightly colored gregarious ones. This change in behaviour is associated with an increase in serotonin. Once local aggregation reaches a critical density, the locusts suddenly start to swarm, as a result of locust-to-locust contact. By using self-propelled particle models from statistical physics, Dr. Simpson and his collaborators showed that this decision to migrate does not involve leader locusts, but is the result of local interactions between individuals. Furthermore, the animals' powerful appetites for protein maintain the swarms. Indeed, were a locust to stop it would be cannibalized by the others. Finally, state-space geometric models of nutrition have shown that this hunger for protein is common to all animals, humans included, and that it can both foster and assuage the development of obesity. In addition these models show that there are costs to protein consumption, and that the prevailing view that caloric restriction prolongs life is incorrect, for insects at least.

A primer of swarm equilibria
Andrew Bernoff (Harvey Mudd College)

Dr. Bernoff talked about the equilibrium configurations of swarming biological organisms subject to exogenous and pairwise endogenous forces that arise from continuous models of population density. By applying a variational method (energy method) to the continuous model, Dr. Bernoff and his collaborators derived sufficient conditions for the extrema to be local minimizers, global minimizers, or minimizers with respect to infinitesimal Lagrangian displacements of mass and analysed the stability of the equilibria. The equilibria were also found to satisfy a Fredholm integral equation, which yielded analytical solutions to the model under certain conditions. Furthermore, the equilibrium solutions were typically compactly supported and often contained jump discontinuities at the edge of the support. Dr. Bernoff applied these methods to a quasi two-dimensional locust model in which the repulsive potential and gravity yielded realistic patterns of aggregation, i.e. a concentrated ground population is separated from an airborne population.

From democratic consensus to cannibalistic hordes: the mechanism and evolution of collective behaviour
Iain Couzin (Princeton University)

Dr. Couzin reported recent progress toward understanding the mechanisms and evolution of collective decision-making in animals. He introduced a mathematical model that incorporates both social tendencies and individual will that has been used to investigate collective decision-making. Studies using this model have shown that individuals can coalesce personal information by using simple, local interaction rules, and that signalling is not necessary in order to form a collective decision. Furthermore, individuals can shift the decision-making threshold by tuning their individual will. In addition, Dr. Couzin talked about results that pertain to democracy and voting within animal groups. These results indicate that through plausible learning rules individuals with simple interactions can effectively exploit social structures that range from completely democratic to despotic.

The road from individual to group position to the emergence in whirligig swarms
William Romney (State University of New York at Potsdam)

Dr. Romney began by using one of his models to simulate a scenario taken from the recent news in which a group of sardines got lost and died as a result of their inability to escape a marina. He then presented a scientific method for modellers: assumptions in tandem with optimality theory generate expected behaviours, experiments validate mathematical predictions and the assumptions on which they are based, and simulations generate mechanisms that can produce experimental observations. This method was contrasted with alternate ones. He went on to discuss four studies. The first three studies explored the effect of population heterogeneity on patterns of population density within stationary groups, on patterns of population density within moving groups, and the trajectories of moving groups. The final study investigated leadership, quorum sensing, and boundary effects. In the first two studies optimality theory quantified the fitness of an individual's position relative to the group as a function of the individual's parameters. For example, in the first study, optimality theory predicted that hungry organisms should occupy the boundary of the group. Experiments, in which whirligigs were tracked, corroborated the optimality predictions. Models showed that an individual could achieve an optimal position relative to the group by tuning its individual parameters, that is, an individual need not have global information about the group in order to achieve an optimal position. In the third model the same procedures were used to investigate the mechanisms through which a group selects a trajectory in order to best utilize renewable resources and avoid predators. Simulation models suggested that a few biased individuals can determine the direction of the group, that stochasticity and group size have minimal effect on emergent trajectories, that heterogeneous groups exhibit less forward motion, and that heterogeneous groups are less polarized. Dr. Romney then briefly mentioned the goals of the final study, which was still in progress.

Adaptive network and effective forces in collective motion: from toy models to experiments
Cristian Huepe (unaffiliated)

Dr. Huepe introduced several existing models that successfully describe collective animal behaviour in order to illustrate the diversity of models that are used to describe the same biological phenomenon. He then asked, "What are the essential characteristics of the real system that each of these models contains?" Dr. Heupe proposed that this question could be addressed by creating a minimal model that is capable of reproducing the dynamical behaviour of interest. Dr. Huepe presented one such simple adaptive network model that describes insect swarming experiments. The model captures experimental dynamics with just a few equations so that analytical investigations are feasible. Specifically, it reproduces several observed swarm features, including density-driven and order-disorder transitions.

WEDNESDAY MARCH 16, 2011

Collective decision making by honeybees
Thomas D. Seeley (Cornell University)

Dr. Seeley described nest site selection in honeybees as an example of collective behaviour. He explained that a good nest site provides bees with shelter from predators and a secure place to store their food. Dr. Seeley then reviewed the procedure through which bees select a nest site. First, scout bees evaluate potential nest sites in private. The scouts then return to the nest and report their findings in public by performing a waggle dance. Experiments have shown that given multiple potential nesting sites a bee colony can select the best site with 90% accuracy, and that duration of the waggle dance corresponds to the quality of the nest site. Dr. Seeley then reviewed several models that attempted to describe nest site selection with varying success. A model of ordinary differential equations suffered from a false predication. A Leslie matrix model captured the most important swarm mechanisms but did not include randomness, and predicted that bees could select the best site from a group of bad sites. An agent-based model contained behaviour parameters that could be tuned to achieve highly accurate decisions, but the decision making process was slow. Finally an augmented agent-based model showed that decision reliability depends on the tension between individual and social pressures: without social pressure convergence to consensus is slow; without individuality, accuracy is lost. Through both experiments and numerical simulations, the mechanisms behind nest site selection were revealed. Many questions were asked in the end of the talk.

Swarm guidance in Apis florae: making decisions on the fly
Mary Myerscough (University of Sydney)

In this talk, Dr. Myerscough discussed the decision-making behaviour of the little studied Asian red dwarf honeybee (Apis florea). She compared nest site selection in A. florea, which is an open nesting honeybee, to that of its relative, A. mellifera. Both types of bees employ scouts who evaluate potential sites and then report their findings to their colony through dance. The dances of A. florea, however, are more variable and less intense than those of A. mellifera and the swarm may select a site despite the fact that multiple scouts continue to dance, i.e. before a clear winner has emerged. Myerscough used a measurement called the consensus vector to measure the taking off direction and found that the vector reaches maximum length before taking off. This led her to ask if it was possible for the swarm to collectively perform the vector sum in flight? She developed a Zonal model to address the question. Numerical results showed partial agreement with experimental data, and led her to speculate that this particular type of honeybee does not find the best nest site, but rather a good region of forest. Because this bee is an open nester it has many potential nest sites and minimal investment in nest selection.

Cohesive Swarm Behaviour with Information Flow Constraints
Kevin Passino (Ohio State University)

Dr. Passino began by describing his research on honeybees. He then introduced an agent-based model that characterizes group cohesiveness. Specifically, he explained how a Lyapunov approach could be used to determine the conditions under which local agent actions can lead to cohesive group behaviour. Surprisingly, cohesive group behaviour can emerge even when information flow is constrained, sensory information is delayed, and sensory information is noisy. Dr. Passino illustrated these ideas with simulations.

THURSDAY MARCH 17, 2011

Organization and regulation of work in the social insect colony
Jennifer Fewell (Arizona State University)

Dr. Fewell discussed research into the mechanisms through which social insects maintain and establish division of labour. Experiments provide some insight into this question. Specifically, experiments have shown that division of labour can emerge when normally solitary individuals are encouraged to work together. These artificial communities, however, exhibit more pronounced division of labour than naturally occurring communities of social insects. Dr. Fewell also showed that social insect colonies are distinguished from archetypical social networks, which are characterized by decentralization, strong community structure, weak bridging links and the small world property. However, social insect networks do exhibit dominant motifs that are commonly found in social networks.

Paulien Hodgeweg (Universiteit Utrecht)

Evolutionary constraints on social evolution from disease risk
Nina Fefferman (Rutgers University)

Dr. Fefferman discussed evidence that natural selection can shape social structures and determine modes of self-organization. She noted that task allocation strategies are species specific. In particular, workers may perform a single task for life, perform a single task according to seniority, perform an increasing number of tasks according to seniority, or perform tasks at random.

A strategy's fitness is determined by a rate of utility production, a time to acclimate to a new task, and a disease risk. The presence of infectious disease substantially alters the relative fitness of a strategy.

Audience and information transfer in ant societies
Claire Detrain (Universite Libre De Bruxelles)

Dr. Detrain discussed information transfer in the context of ant foraging. She explained that the relationship between exploitation pattern and population density is nonlinear and discontinuous so that sudden changes in exploitation patterns can occur as the population density changes. Ant colonies, however, do not passively undergo such a density-dependent structuring because they actively manage the density of workers. An analytical model is developed to investigate how worker density is regulated. A steady-state bifurcation analysis revealed that prior worker densities could influence the system's evolution. Dr. Detrain discussed mechanisms through which an ant colony stores worker densities in order to improve its foraging efficiency. Finally, she discussed how it is that the number of foragers can influence resource selection when resource availability and quality is variable.

Swarms as smart architects: understanding construction dynamics in ant colonies
Guy Theraulaz (Universite Paul Sabatier)

Dr. Theraulaz began by exhibiting several amazing termite nests. A single nest is approximately 600 times larger than an individual termite and boasts a highly complex structure. The audience then embarked on a 3D virtual termite nest tour, during which Dr. Theraulaz highlighted the nest's large-scale structural patterns. Dr. Theraulaz's explained that his lab has elucidated the mechanisms through which these large-scale patterns emerge from individual behavior by observing only the early stages of nest construction in the ant Lasius niger. These experimental observations were used to identify individual based rules that govern the transportation and deposition of construction material. These rules were implemented in a 3D model. Simulations showed that these individual based rules were sufficient to generate the observed dynamics and large-scale patterns. The model also revealed that complex helicoidal structures, which connect nearby chambers, are the result of continuous construction, that is, a termite nest is a dynamic object through which construction material is constantly cycling.

Guy Theraulaz (Universite Paul Sabatier)

Optimality theory in collective behavior
James Marshall (University of Sheffield)

Dr. Marshall began with the observation that diverse biological systems have converged to the same decision making strategies. He suggested that this observation is interesting because it supports the idea that the underlying mechanisms that produce these strategies are optimal. He went on to briefly review the application of optimality theory to evolutionary biology. Dr. Marshall then came to his central point, which was that collective insect behavior expands optimality theory in interesting ways. He illustrated this point with an example, in which an optimality model was applied to the problem of nest site selection in bees. The model in question was based on neuroscience experiments that indicated monkey brains form decisions so as to optimize the speed-accuracy tradeoff. When applied to bees, however, the model was clearly suboptimal as it predicted that the bees would be unable to choose between two identical nest sites. After incorporating a stop signal into the model, so that avocation for one site inhibited avocation for the other, the bees were able to quickly choose between the two sites. Simulations suggested that individual based rules allow the bees to select a nest site quickly if their options are effectively identical, and to optimize the speed accuracy trade-off if their options are significantly different. It follows that in either case the bees optimize their reward rate. Thus, the application of an optimality theory model to collective insect behavior led Dr. Marshall to rethink the model's original optimality criteria.

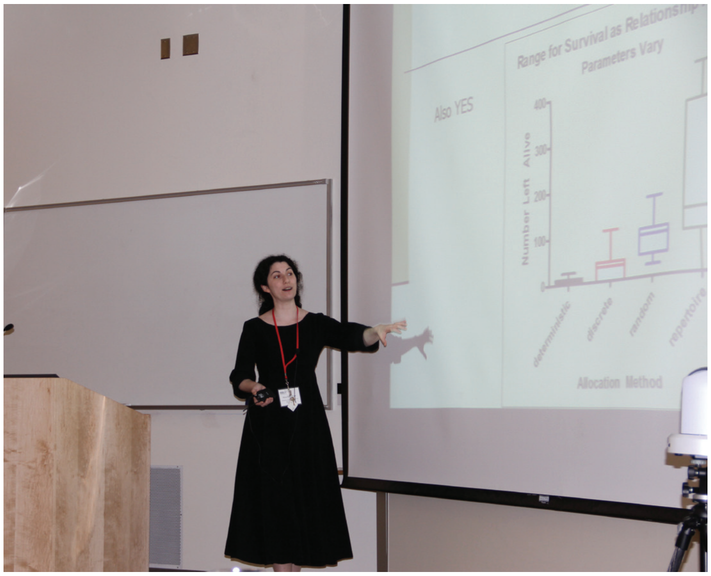
FRIDAY MARCH 18, 2011

Network topology and the evolution of collective migration
Naomi Leonard (Princeton University)

Dr. Leonard began by presenting several videos of interesting collective behavior. She went on to address how it is that network topology alters the accuracy of consensus decisions and influences evolutionary migration? By employing agent-based models, Leonard and her collaborators showed that a small group of leaders, who are sensitive to environmental cues, could successfully guide a larger group of followers, who are sensitive to social interactions. In addition, simulations have shown that when the cost of leadership is high the speciation of a homogeneous group into leaders and followers is a stable evolutionary. Analytically tractable mean-field models were used to corroborate these observations.

Engineering self-organizing systems
Radhika Nagpal (Harvard University)

Many biological systems are maintained by vast numbers of cheap and unreliable individuals who cooperate to achieve complex goals. Engineers are rapidly designing synthetic distributed systems that conform to the same basic paradigm. Although much research has focused on the emergence of global phenomena little effort has been made to deduce effective individual rules from observed global features. This question is of paramount importance to engineers and is the focus of Nagpal's lab. In this talk, Dr. Nagpal described several of her projects, including the design of simple robots capable of building structures without explicit communication, self-adaptive modular robots that can respond to the environment, and wireless sensor networks that use firefly-inspired algorithms to achieve high throughput. In each case, the laboratory's simple and decentralized designs were inspired by biology. Techniques from computer science were used to analyze and generalize algorithms to in order to perform new tasks.



Nina Fefferman (Rutgers University)

Social insects and organic computing: bee nest-site selection and task separation model and optimization
Martin Middendorf (University of Leipzig)

Dr. Middendorf discussed nest-site selection based optimization algorithms, and related attempts to model nest-site selection. He began by presenting a detailed model of nest-site selection. The model was evaluated through simulations in which the nest-site quality was varied. In particular, it was shown that the bees could select a mediocre site over a site that was better at times but worse at others. The model was refined to produce an optimization algorithm called the bee nest algorithm. The algorithm was applied to the ligand-docking problem in which one wants to find good docking place for a small ligand on a large protein. The bee nest algorithm was shown to outperform existing algorithms.

Dr. Middendorf went on to discuss response threshold models. These models are applied not only to the study of task allocation in insects but also to computer systems that distribute stocks. He presented a spatial model in which ants, who were characterized by dynamic response thresholds, were subjected to stimuli to perform tasks. The model was judged according to its ability to maintain low stimuli, i.e. to keep up with all the tasks. The model was found to work well when the tasks were separated in space. This observation inspired Dr. Middendorf to introduce a new task, sorting. The augmented model outperformed the original.

Multi-Level Modeling and Distributed Control for Miniature Robotic Swarms
Alcherio Martinoli (EPFL ENAC IIE DISAL)

Dr. Martinoli began by reviewing several case studies, in which his group designed models of collaborative work in robots. These models were used to understand the interplay between the system's components, to optimize designs, to predict how well a proposed system would perform, to determine how a system would perform in conditions that are difficult to produce experimentally, and to formally analyze a system's stability. Dr. Martinoli went on to describe the experimental features and modeling assumptions that were incorporated into a general protocol for producing specific multi-level models. This protocol was illustrated with concrete examples. Finally, Dr. Martinoli contrasted multi-level modeling in biology and engineering, and concluded with a description of some open challenges in the field.

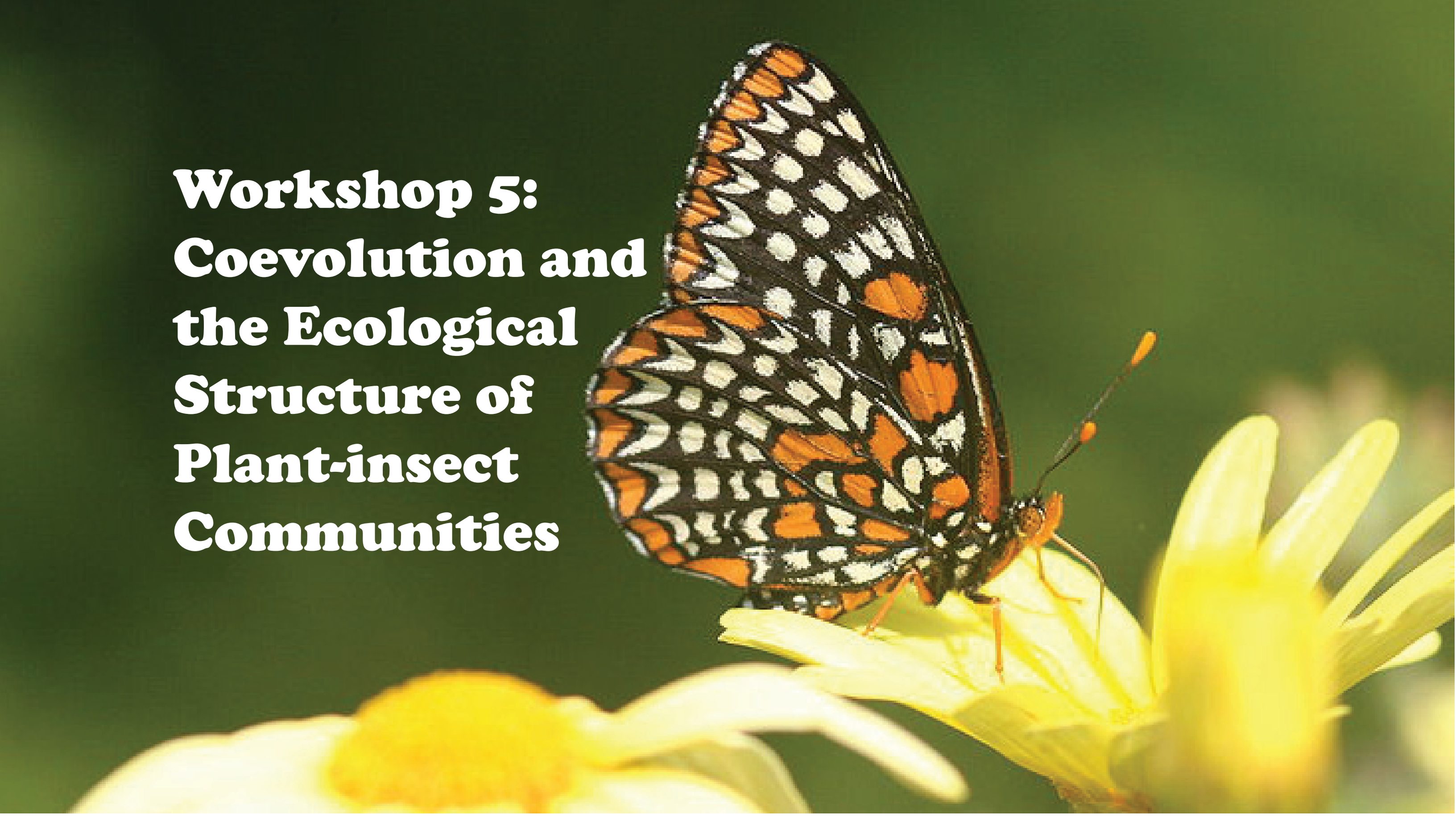
No title available
Craig Tovey (Georgia Institute of Technology)

Dr. Tovey began by describing the process of web hosting, in which businesses outsource the maintenance of servers. Web-hosters are paid a fee for each transaction that they process. Web-hosters attempt to allocate servers in a way that maximizes revenue. This is, however, a challenging problem, because security concerns restrict the applications that can run on a single server and demand that servers be scrubbed between applications. These difficulties are confounded by demand variability. Honeybees face remarkably similar problems in deciding which flower patches to exploit. Interestingly, the honeybee's solution to this problem is not optimal, but near optimal. Dr. Tovey designed a honeybee-based algorithm to address the web-server allocation problem. He compared the algorithm's performance with that of three other algorithms, an omniscient algorithm, a greedy algorithm, and an optimal-static algorithm. The honeybee-algorithm was found to outperform all but the omniscient algorithm.

Variational Principles and Control of Collective Behavior
P. S. Krishnaprasad (University of Maryland, College Park)

Dr. Krishnaprasad began by describing his basic modeling framework, in which self-steering particles interact via a system of differential equations. These particles can represent prey and predators. Predators can employ a variety of strategies including classic pursuit, constant bearing, and motion camouflage in the pursuit of prey. Each strategy is associated with a contrast function that measures how close the predator is to obtaining the strategy. Dr. Krishnaprasad showed that a model in which three particles employ the constant bearing strategy feedback law exhibits periodicity. These results led him to wonder if periodic solutions could emerge from a model that incorporated individual or collective optimality considerations. Dr. Krishnaprasad applied open loop control to these models in order to address this question.

Workshop 5: Coevolution and the Ecological Structure of Plant-insect Communities



APRIL 4-7, 2011

Organizers: Scott L. Nuismer (University of Idaho) and Sharon Y. Strauss (University of California, Davis)

Report written by Sam Handelman, Deena Schmidt, and Rebecca Tien

MONDAY, APRIL 4TH

Recognizing Coevolution
Sharon Strauss (University of California, Davis)

Strauss's talk was divided into 3 main points. The first point briefly addressed is that recognizing coevolution in the real world can be quite difficult. There are a number of reasons why this might be true. If for example an insect does not eat a plant does this mean that no interaction exists, or that a coevolutionary relationship existed sometime in the past but that the plant "won" the arms race? She refers to this as "the ghost of coevolution past". This raises the question of how one can distinguish between losers and non-players. Plants that insects are not feeding on may be a result of evolutionary history whose current absence of relationship makes the interaction difficult to see.

The second point was the role that community complexity might play on the interaction of two coevolving species and how community complexity can be destroyed by the introduction of non-native invasive species. For example, there is a known coevolutionary relationship between crossbills (a type of bird) and conifers. Foraging by crossbills on pine cones over time has led to the development of larger, thicker-scaled cones in mountain ranges where red squirrels are absent. In turn, crossbills in this region are larger-billed than crossbills that coexist in regions where red squirrels exist. However, when red squirrels are introduced in the mountainous environment, these larger-billed crossbills become practically extinct. The diversifying coevolution seen in the system that allows for diversity in crossbill phenotypes relies on geographic variation in the distribution of strongly interacting species. The outcompeting of crossbills by the introduction of the invasive red squirrel led to a less complex community structure. In general, species introductions can lead to a reduction in community complexity because introduced species have not evolved a relationship with other organisms in the environment that might reduce fitness (reduction in fitness is often a consequence of investing in a coevolved trait). These introduced species have less constraints imposed on them from conflicting selection. As a consequence, they can outcompete other organisms in the environment and reduce species richness in a given area.

The last point made is that strong interactors in a community can cut through the Gordian knot of community complexity and, as a consequence, make recognizing coevolutionary interactions easier to spot. A strong interactor is often any force to which the system is evolutionarily naïve. When you introduce an organism to a community where mutual adaptation has not evolved, that community can have a disproportionally large response to the invader. One of the best examples of this is anthropogenic impacts on a population or community. For example, harvesting of Cod in the North Atlantic over time has led to a 20% reduction in size of mature individuals at time of 1st reproduction.

Red King predators, evolution of mutualistic antagonists and coevolution patterns between mutualists and antagonists

Claire De Mazancourt (McGill University)

Most of the work presented used a general predator-prey model, but it was pointed out that the same model could be applied to plant-insect interaction. De Mazancourt's main question was the effect of rapid evolution of a predator on the dynamics of the interaction. The model includes density dependence for both the prey and the predator, and the predator can either be specialized on prey or have alternative prey with growth term independent of prey being modeled. The interaction term (i.e. functional response) depends on traits of both prey (u) and predator (v). The model considers the case where the species evolve so that their traits are matched. A matching interaction term is strongest when the difference between u and v is zero. The biological example given is the case of a cuckoo whose eggs need to match the host in order for them to be accepted. In her models, the assumption of fast ecology and slow evolution is made so that one can justify the use of Adaptive Dynamics. In the model, there are two outcomes: either the exploiter catches up (the prey runs slower than predator) or the victim escapes (evolves faster). Strength of interaction is either maximum or minimum depending on who's evolving faster. What determines the outcome involves two ratios: the ratio of evolutionary rates and the ratio of interaction impacts (incentive to run, i.e. benefit or cost of evolving). Simulations give unexpected results due to fast evolution. Specifically, the predator has lowered interaction strength (lower predation rate) with prey, which is detrimental to the predator. When the predator "catches up" with the prey, the prey is at a fitness minimum, which cannot happen when evolution is slow. Coexistence happens when the predator is fast because the predator shifts back and forth to whichever prey type is more abundant. When predator evolution is fast, large mutations in prey mean that eventually one eliminates the other. If mutations are small, then one can get branching of prey types and both coexist. This type of predator evolution driven interaction is referred to as Red King dynamics: it pays for the prey to be slow-evolving relative to the predator. Fast evolution of the predator enables both coexistence of different prey types and decreased predation rate. If one prey type evolves to become a specialist, the predator responds by evolving higher predation rates. If coexisting prey are both generalists, then the predator oscillates between both prey types and evolves lower predation rates.

Exploring the interplay between ecology and evolution of plant-herbivore interactions

Marc Johnson (University of Toronto)

Marc's research focused on how ecological interactions within communities drive evolution. He offered two general hypotheses for looking at the interaction: 1) community ecology influences evolution, 2) genetic variation and evolution within a population shapes community dynamics. Most of his work involves plant-herbivore interactions, in part because these are some of the most dominant interactions on earth. Herbivores consume such a large percentage of plant NPP that they impose very strong selection for plants to evolve a variety of defenses. In his research, Marc tries to understand how selection by herbivores drives these defense traits. To look at this, a series of questions were asked: 1) Is there genetic variation in plant defense that is heritable?; 2) Does this variation affect resistance to herbivores?; 3) Is there also selection on resistance traits in the herbivore?; and 4) Does selection by herbivores drive evolution within populations? In other studies, there is much evidence for the first three questions, but not much convincing evidence for question four. The main goal of Marc's research was to try to address this gap by examining both insect and mammalian herbivory on the common primrose (a model organism that reproduces asexually and has multiple herbivore interactions).

The first experiment created 16 populations identical in size and structure. Each population had 20 genotypes uniquely determined via microsatellites. Each genotype started at the same genotype frequency. In half the populations, insecticide was used and in the other half, herbivory was allowed. Once a year, the populations were censused to look at changes in genotype frequency. Data collected allowed the researchers to determine whether there was divergence between populations in genotype frequency. One would expect the relative frequency of genotypes to be the same between the populations if there was no response to different treatments. Of the 20 genotypes, some rapidly increased over 3 years of data, some decreased and some changed not at all. With these results it is difficult to determine what the overall effect is. To remedy this problem, multivariable statistics were used to compare all genotypes at the same time. It was found that herbivores, as compared to control group drove divergent adaptive evolution of these populations.

The second experiment, looked at the effect of rabbit herbivory on plants. In this system, plots were created that excluded rabbit herbivory over many generations. Nearby plots were naturally exposed to continuous herbivory for hundreds of years. It was predicted that the relaxation of selection in the exclusion plots would lead to a decrease in selection. The study focused on a number of traits such as intrinsic growth rate, tolerance (ability to mount response to damage), and chemical resistance. The researchers found no evolutionary change in expected chemical resistance traits and no change in tolerance (expected rapid response here). They did however see very rapid evolution of intrinsic growth rate and a decrease in growth rate as the time since last rabbit herbivory increased. The explanation for the last result is that fast growth rate has a cost and hence is lost when no longer needed as a response to herbivory.

Evolution of growth rate is often assumed to be independent of herbivory and is thought to constrain evolution of defense. To push current thinking about this aspect of coevolution the following ideas were offered forth: Although the evolution of growth rate is viewed as being independent, it might be the direct target of natural selection. If so, then one of the most base assumptions in models is often violated; Defense appears to be controlled by a wide variety of complex traits beyond the traditional chemical and physical defense traits considered in models (i.e. models do not accurately capture

the complexity of the natural world.) These two experimental results address the first hypothesis previously posed (i.e. species interactions affect trait evolution). In the last part of the talk, the second hypothesis is focused on impact of evolution on community ecology. There is ample evidence that all populations contain genetic variation. It is interesting to look at plant-insect interactions because any genetic change in plants should lead to cascading changes in the community given their position at the base of the food web. He addressed two questions to examine this hypothesis: 1) does plant genotype affect the ecology of arthropod populations and entire communities? and 2) can evolution in plant populations drive long term ecological changes in a community? The approach taken in answering these questions was both experimental and theoretical. He found that the plant genotype does indeed affect the herbivores in the system as well as predators and mutualistic species of the herbivores. The affect of genotype can have an even larger impact than inter/intraspecific competition and habitat on structuring the community. The last item discussed was the existence of evolution in one population can drive ecological dynamics observed in another. To look at this experimentally, there has to be both genetic variation, directional selection on plant traits and furthermore, these traits must affect variation in community. The first two conditions are a part of measuring evolution by natural selection. The third condition can be looked at by how some community variable is correlated with a particular plant trait under selection. Johnson experimentally tested a number of predictions again using evening primrose and an arthropod that specialized in this plant. He showed that evolution of a particular known defense trait in the plant can in fact shape the ecological dynamics of the herbivore. In summary, through both experimental and theoretical observation it was shown that plant genotypes have bottom-up effects on both herbivores as well as the entire community and that rapid evolution of plant defense can drive ecological dynamics of herbivore populations. Several implications of these results: due to the rapid evolutionary response of herbivores, it is possible to conduct experimental evolution in the field; we can use theory to test not only predicted patterns of interaction, but also the eco-evolutionary processes underlying those patterns; and last, some of the current assumptions might be over simplified.

Estimating selection in interspecific interactions: theory and practice

Ben Ridenhour (University of Notre Dame)

Ben started his talk with a discussion of the theory behind the Selective Source Analysis (SSA) method. Mathematically, selection is defined as the difference between the mean phenotype of the population at time t and time t+1. The mean can be found by looking at the integral of the mean multiplied by its distribution. Another way of seeing this is that selection is the covariance between fitness and phenotype. In reality, a given species fitness is a function of not only its own phenotype, but the phenotype of the species it interacts with. The interaction can be viewed as a fitness surface, and we can also express fitness as a polynomial function representing covariance of the two interacting species. The polynomial has three components: selection not due to interaction, selection due to assortative interactions, and selection due to interactions determine by z (individual's fitness) and z' (fitness of interacting species). In practice there are a number of steps for using these equations to run SSA described as follows: 1) Get data, 2) Fit a polynomial to the data to generate the components of the polynomial described above, 3) Use these sub functions to predict the proportion of relative fitness related to each one of them, 4) Approximate the selection differential, 5) Calculate p inverse, giving selection gradients, and finally, 6) Determine confidence intervals.

Martin Heil (CINVESTAV - Irapuato)

Once the basics of SSA were described, a real study system was discussed employing these methods. The experimental study looked at divergence in a Salmon River plant known as Heuchera grossulariifolia. This particular plant can have a flowering phenology that is either tetraploidy or diploidy. An initial study showed divergence in a number of traits (average scape length, averaging flowering date, maximum floral display) between the two types. A few hypotheses for divergence include competition, intercytotype mating, and interactions with other species such as the parasite, G. politella, in the community (favored hypothesis). Three hundred plants were collected and plant traits involved in fitness were measured. G. politella are at their highest abundance when the plant is flowering so it could act as a force for divergence. Once data were collected for this system, SSA was performed. For this analysis a number of parasite traits were used -- was flower attacked, proportion of capsules attacked, total number of eggs and larvae found in each plant. Analysis indicated a greater attack rate on tetraploids than diploids and also a greater number of parasite eggs and larvae. In general, diploids have higher fitness and the selection attributed to G. politella was found to be large. Ridenhour found that the tetraploids flower earlier to get away from parasites, and the diploids flower later for the same reason, thereby driving divergence between the two phenotypes.

Some benefits of using SSA are that it provides an easy way to estimate the effect of a particular agent on selection in a population, it builds upon pre-existing methods of analysis, data requirements are not too stringent, analysis can be easily accomplished using programming packages such as R, and finally, the method has been successful in analyzing a number of real world systems.

The plasticity load: The cost of flexibility in a variable environment

Michael Wade (Indiana University)

Wade started off with a general description of adaptation and additive genetic variance to build a platform for discussing phenotypic variation in populations as well as phenotypic plasticity.

Adaptation can be thought of as the impact of selection acting independently at each locus. An individual's total phenotype is described by the sum of the contribution of each one of these genes, (a.k.a additive genetic variance). Wade cites three different conditions which favor the evolution of phenotypic plasticity: 1) varying levels of natural selection between different environments, 2) significant genotype x environment interaction in the population, and 3) some triggering environment that turns on genes not normally on in order to optimize gene expression for high fitness. Common examples of these last types of adaptive genes are genes that aid in defense against a threat such as a virus or pathogen, and genes that offer an escape mechanism from extreme environments such as drought and sexual reproduction genes. These conditionally expressed genes can show up in different ways: expressed by only a small fraction of the population, expressed by all individuals, but only for a few generations, or expressed only by a few individuals for a few generations. Because these genes are conditionally turned on by the environment, selection for them is relaxed as opposed to other types of genes. Variation arises by mutations and mutation-selection balance determines variability at the gene level. The prediction is that within species, these conditionally expressed (i.e. plasticity) genes should be more polymorphic than their constitutively expressed counterparts. In fact, the less frequently these genes are turned on, the higher the relative polymorphism at equilibrium. The problem with these types of genes is that if a new beneficial plasticity mutation arises, the probability of fixation of the gene in the population is very small. A second prediction is that between species, plasticity genes should be more divergent from one species to another than its constitutively expressed counterpart. These two predictions were both tested by Wade by looking through available databases from past experiments. Both theoretical predictions were shown to be correct. In conclusion, the expression of plasticity genes occurs in response to particular environments. These genes are under reduced selective pressure because although many copies get passed down from generation to generation, they are not generally expressed so most of the time there is nothing for natural selection to act on. As a consequence of this, these types of genes are more polymorphic between species and divergent between species.

Sharon Strauss (UC Davis)

TUESDAY, APRIL 5TH

Trait matching: What does it tell us?

Bruce Anderson (University of Stellenbosch, South Africa)

The main focus of Bruce's talk was the matching of morphological traits between interacting species and what it means in terms of coevolution. A biological example of trait matching is proboscis length of flies and tube length of flowers. He also talked about Darwin's Ancraecum Orchid, called such because Darwin was sure that the tube length of the flower suggested that a moth pollinated it with a long proboscis despite never having seen such a moth. He, along with Wallace were so sure of this that Wallace drew a picture of how the moth might appear. Eventually, the moth was indeed found. One might ask, "What made Darwin make this prediction?" The answer appears to be that there is selective pressure for the orchid to evolve tubes longer than moth's tongue which forces the moth to push up against reproductive parts of the orchid in order to access nectar. Moths correspondingly want to evolve tongues long enough to reach the bottom of the nectar.

One would expect to find geographically variable traits matched at the population level. Bruce and his colleagues looked at geographical variation of tube length of flowers in Dahlberg. They found significant variation in proboscis length of the fly that feeds on their study orchid. These patterns of trait matching are quite common and found in several systems. One can get patterns of trait matching even when organisms are not coevolved (flower evolves longer stem to be pollinated by the bee, but the bee can remain unaffected by the length of the flower stem).

Bruce and his fellow researchers wondered whether patterns of trait matching seen in nature arise through selection or instead are a result of similar gene flow patterns for both species. For example, orchids that are geographically close and genetically close can have very different tube lengths. This implies that variation is not a result of gene flow but rather, selection. They also wondered about the impact of biotic vs. abiotic factors as selective pressures. Abiotic factors such as altitude might generate variation in tongue length, but not tube length differences. This is because there is a constraint on tongue lengths at greater altitudes as a result of extreme costs at higher altitude. A ceiling is put on the evolutionary race as a result.

It turns out that trait matching can be the result of EITHER coevolution or unilateral evolution. The abiotic environment can be very important, but community composition can also play a role. The net selective pressure (other things in the environment) can cause one of the organisms in the interaction to be pushed more to an extreme than the other. This leads to a number of questions: Does this end up breaking the interaction? Why are insects on the losing side? Why is selection stronger for plant traits? In nature, one often sees asymmetric dependence, where plants are much more likely to be specialists and pollinators likely to be generalists. Self-pollinators (not exclusively) have less exaggerated traits relative to the insect. Another cause for the asymmetry found in the eco-evolutionary interaction is that there are stronger foraging constraints against insects (i.e. higher costs for longer tongues). Future directions to be looked at include reciprocal selection, effects of abiotic environment, and the cause of trait mismatches.

What do studies of local adaptation and trait matching reveal about the coevolutionary process?

Scott Nuismer (University of Idaho)

Coevolution is most often defined as reciprocal selection, but whether reciprocal selection is actually occurring can be difficult to determine in a real world setting. There are two indirect approaches that can be used to determine the existence of a coevolutionary interaction. The first method is to establish covariance between traits of interacting species (a.k.a trait matching) where a positive correlation implies the existence of coevolution. The second method is to establish local adaptation through reciprocal transplant experiments. The goal of Nuismer's work is to unify these two approaches.

In trait matching, the strength of coevolutionary interaction is inferred from the estimated correlation between traits and the focus in on a single pair of traits (e.g. a defensive trait by a plant and a matching resistance trait by its herbivore). For adaptation studies (i.e. reciprocal transplants), the strength of selection is inferred from a composite quantity and the number of traits involved in the interaction is unknown. Models can be used to answer the following questions: 1) Is coevolution sufficient for generating correlations? 2) Is coevolution necessary? 3) If it is sufficient, but not necessary, how does one proceed from there? The model must be able to predict the correlation between traits among replicate populations.

In order to predict the existence of coevolution, one must calculate the mean fitness using the Quantitative Trait (QT) method. This gives both the direction and the strength of selection. The first step is to define fitness, where the fitness is described by both the impact of the abiotic environment (optimal phenotype favored by the environment as well as the role that the interaction with another organism has on an individual's fitness. There are two types of interactions, either phenotypic matching (if the interaction is beneficial, it is best to match your trait with the trait of the interacting organism) or phenotypic differences (whether you are harmed or not, it is always better to invest "more" in a particular trait). The model assumes weak selection and gives a prediction for the change in mean trait, which depends on abiotic constraints, biotic selection (phenotypic matching/differences), and genetic drift. At a local scale, it is predicted that in the case of phenotypic matching, if the interaction is mutualistic, then there is stable selection. If it is antagonistic then there is either coexistence or the emergence of stable cycles. In the case of competition, one sees either stabilizing selection, or divergence. The prediction for phenotypic differences states that stabilizing selection occurs in all types of interactions.

In theory, it would be great to have a model of many populations across space with gene flow (think island populations). However, this leads to a very large number of equations, which is in most cases impossible to analyze. Instead, metapopulations can be described using statistical moments rather than looking at individual trait means within a population. The advantage is that no matter the number of interacting species being explored, the whole system can be described using 5 moments and 3 equations. With this method, one can track global changes (e.g. tongue length across all species) across space and look at the covariance between traits. Using this method, the predictions are as follows: phenotypic matching will either yield the evolution of a stable equilibrium or runaway coevolution (i.e. divergence), whereas the result of phenotypic differences is evolution of a stable equilibrium where the covariance equals zero. They find that only interactions mediated by phenotypic matching actually cause correlations to evolve. The results depend on a number of assumptions including weak selection, fixed additive genetic variance. These assumptions can be relaxed using individual based models. They find that in the phenotypic matching case both mutualism and antagonism have strong correlations caused by coevolution. This is also true for competition and commensalism. In the phenotypic difference case they got positive correlations that were not predicted by analytic results.

In summary, Nuismer and his fellow researchers found that coevolution can cause strong correlations between traits of interacting species, but for many parameter combinations, coevolution does not case correlations. Another point is that other ecological processes such as evolutionary commensalism can generate these correlations. The main take home message is that coevolution cannot be inferred from trait matching or local adaptation approaches alone.

Frontier Mutualism and Community Genetics in Attine Ants and their Cultivated Fungi

Ulrich Mueller (University of Texas, Austin)

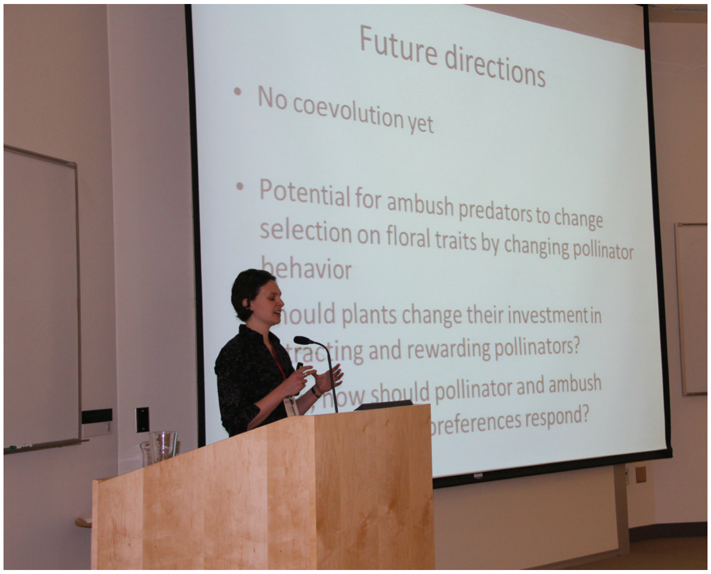
Mueller presented an analysis of a series of field observations on farming ants, and the implications of these observations for the evolution of the ants and their cultivated fungus. First, the cultivated fungi and their close relatives, but not their "wild" cousins, have a physical shape favoring harvesting by the ants, which is a priori evidence of co-evolution. The ants are completely dependent on their fungal symbiont, and have a number of highly specialized behaviors, including specialized mouth parts allowing the ant queen to safely transport fungus to newly founded gardens. Fifteen years ago, Mueller's group tested the hypothesis, which was widely presumed true since ant-fungus mutualism was discovered in the 1860s, that the fungus was exclusively vertically transmitted by this mechanism; phylogenetic reconstruction was inconsistent with this co-speciation hypothesis, but does show an association between large clades, which equate with the vegetable source on which the fungus are grown. Thus, a potato-specialist ant can alternate between fungal strains which grow on potatoes but cannot grow fungus on maize, and vice versa. While the ants are entirely obligate symbionts, some but not all of the cultivated fungi are capable of surviving as free living organisms as well. Those fungi which cannot maintain a free living existence do, apparently, co-speciate with their ant symbiont. Phylogenetic reconstruction from microsatellite DNA in the fungus show that the fungus within each leaf cutter ant nest are clonal, as do the pellets of fungus from individual ant queens which depart from a given nest. These clonal ("monoculture") gardens are vulnerable to disease, but the symbiotic ants have numerous adaptations, including tending behaviors and antibiotic saliva, which they use to defend their gardens from parasites. These antibiotics are produced by yet another group of putative symbionts, Pseudonocardia bacteria which live in the ants' cuticle. Mueller's group have produced numerous findings which conflict with widely held presumptions

regarding these bacteria, however: the bacteria are not vertically transmitted (as had been believed) but are found on both males and females; the bacteria are not found in all species of Attine ants; the bacteria are found in populations which are not parasitized by the common parasite, implying the bacteria serve some other function in those populations; the bacteria are closely related to free-living forms of Pseudonocardia, which is inconsistent with co-speciation and obligate symbiosis; and, finally, the Pseudonocardia population found on individual ants can be highly diverse. There is considerable dissension in the community regarding what symbiotic role these cuticle bacteria may play, if any. Other "auxillary" microbes within the garden may contribute to disease resistance.
The talk includes a review of other analogous systems of symbiotic microbes found in plants, algae and elsewhere, implying broad applicability to the underlying question. To test the phenotypic impact of these symbionts, Mueller's group studied different combinations of fungi and asexually reproducing ants. Asexual reproduction simplifies the genetic impact of the ant in the experimental system. Mueller emphasizes the need for new methods and approaches to identify phenotypic effects of different bacterial communities.

Finally, in a distinct group of results, Mueller's group has found genetic differences in cultivated Fungi along the edge of the region through which these leaf-cutter ants are expanding (in central Texas). In relatively cold climates, the cultivated fungi is more cold tolerant, and this cold tolerance appears to be heritable based on genetic comparisons.

Exploring selection mosaics and coevolution in multiespesific generalized systems
Jose Maria Gomez (Universidad de Granada)

Gomez presented a series of field results on the evolution of "generalist" pollinators and the corresponding plants. This is unusual in the field, which generally concentrates on interaction-mediated selection in specialists. The data collected is very impressive, and includes observations of individual pollinators moving between different flowers of genus Erysimum, as well as fitness measurements based on the number of seeds produced by the corresponding flowers. Erysimum was chosen because it is a major generalist, associated with hundreds of different pollinators. Within each Erysimum population, there was, as expected, optimization of the floral traits to optimize pollination by the major pollinators. The effect of these genetic optimizations was confirmed by transplanting different Erysimum between environments with a different mixture of available pollinators and quantifying the effect on fitness. However, each Erysimum species remains somewhat generalist, which requires new approaches to quantify the effect of co-evolution on floral fitness, since one cannot measure co-speciation with a single pollinator. Furthermore, this requires some revision to predominant evolutionary theory, which tends to predict that specialists will be more fit than generalists under the observed pollination scheme. Dr. Gomez represents the movement of individual pollinators (extensive data collected as noted) as a bipartite network between plants and pollinators. Note that this is a network between plants and individual pollinators observed in the actual data.



Emily Jones (Washington State University)

This is then transformed into a unipartite network where plant species are connected according to the individual pollinating insects which they share. Modules within the network indicate plant species which share many pollinators. These modules is then mapped onto the phylogeny of the Erysimum and show that geographic constraints increase the fitness of generalist plants, implying that the specifics of geography allow plant species to maintain the generalist phenotype.

A coevolutionary resolution to the paradox of concave selection?
Paul Hohenlohe (Universiy of Oregon)

Hohenlohe presented a partial resolution to an outstanding issue in evolutionary modeling – when observed on short time scales, the evolutionary landscape is generally "concave", that is, most organisms are some distance from an observed fitness maximum, so that populations are generally in motion, in a genetic/evolutionary sense. However, the observed genetic movement over short time scales seems inconsistent with evolutionary rates reconstructed from comparative data over longer time scales. It is proposed that co-evolution may resolve this apparent paradox, and mathematical models are shown which are consistent with this resolution.

Bursera and Blepharida: The ecological play and the coevolutionary theatre
Judith Becerra (University of Arizona)

Becerra discussed the chemical diversity among the presumptive pesticide compounds produced by plants of genus Bursera in different contexts, and how the relative degree of observed chemical diversity may relate to features of the plant community including size, dispersal and the diversity of associated herbivores, especially beetles of the genus Blepharida. Particularly in the smallest communities of Bursera, located at low altitudes at the bottoms of the valleys where they are found, the plants within each community were significantly more chemically diverse than random replicates of the same size from the overall population of plants. At higher altitudes, where the plant population is sparser but attack by Blepharida is rarer, the chemical diversity among Bursera within each locale declines to roughly random expectation. There is an overall highly significant correlation between attack by these specialized insects and within-community diversity of plant chemistry. These results are then compared to the calibrated phylogenetic tree of Bursera, and the origin of each chemical compound is located on the phylogenetic tree. Because they have inferred a relatively low rate of extinction in Bursera species, the relative rate of speciation and chemical diversification can be calibrated. Surprisingly, during the relatively recent "burst" of speciation, since roughly 40 m.y.a., the rate of novel chemistry has slowed, but the rate of change in the relative concentration of different compounds has increased; and, species with a similar complement of protective chemicals have become geographically distinct.

WEDNESDAY, APRIL 6

How multi-trophic interactions shape biodiversity in space
Franck Jabot (Center for Disease Control & Prevention)

Jabot presented a mechanistic model of spatial network dynamics focusing on multi-trophic interactions and spatial community structure. He studied the properties of this model by simulation and also compared the model to real network data using a technique called Approximate Bayesian Computation. Jabot emphasized the need for mechanistic models of network dynamics that are built from trait-based rules and involve spatial effects. In particular, he focused on mutualistic and antagonistic bi-partite networks independently (i.e. plant-pollinator or plant-herbivore). Their model is based on the work of Santamaria and Rodriguez-Girones (2007): each plant and animal species has a set of traits that are randomly drawn and two types of trait-based interaction rules (a matching rule and a threshold rule for the animal and plant traits). This is a Wright-Fisher like model with non-overlapping generations that yields stochastic dynamics. Jabot asked two main questions: 1) How are multi-trophic interactions likely to impact the composition and dynamics of the plant group? 2) How does the effect of one trophic group on the other depend on network properties and spatial structure? The answer to 1) is that the impact of variation is not always the same. He described an example with mutualistic interactions using the threshold rule showing that both positive and negative effects on community richness are possible. Moreover, their finding that the architecture of mutualistic networks increases local biodiversity is in agreement with recent studies. The interpretation of this result is that multi-trophic interactions have both a filtering and a stabilizing effect, whereas the summed impact depends on the balance between these two effects. The short answer to 2) is that the specificity of the interactions increases the filtering effects and dispersal limitation increases the stabilizing effect. They also looked at beta-diversity of plants (which is metacommunity plant richness/ local plant richness) and found that the interactions had the opposite effect. In particular, when the interactions are filtering the plant communities, there is a positive effect on beta-diversity. Finally, Jabot discussed the Approximate Bayesian Computation method (Beaumont et al., Genetics 2002) to parameterize their model using real data. He characterized the properties of the simulated networks (specifically nestedness and specialization), retained simulations which are closest to the data, and obtained an estimate of the model parameters which best fit the data.

Complex networks of interactions and coevolution in multispecific assemblages of free-living species
Pedro Jordano (Integrative Ecology Group, Estacion Biologica de Donana, CSIC)

Ecological interactions among plants and animals are the backbone of biodiversity. Interactions take a tremendous variety of forms in nature and have pervasive consequences for the population dynamics and evolution of species. Pollen and seed movement are the primary outcomes these interactions, yet we know very little of how these highly complex webs of mutualistic interactions coevolve and what are the consequences of these diversified mutualisms. Jordano noted that a persistent challenge in evolutionary biology has been to understand how coevolution has produced complex webs of interacting species, where a large number of species interact through mutual dependences (e.g., mutualisms) or influences (e.g., predator-prey interactions in food webs). Recently, it has been shown that these interactions can form complex networks involving dozens and even hundreds of species. These coevolutionary networks are highly heterogeneous, with a core of super- generalists, nested, asymmetric, and contain multiple modules that act as the basic blocks of the complex web. Jordano explored how the past evolutionary history conveyed in the phylogenies of plants and animals can explain these network patterns and the robustness of the network to species extinctions. Because phylogenetically similar species tend to play similar roles in the network, extinction events trigger non-random coextinction cascades. This implies that taxonomic diversity is lost faster than expected if there was no relationship between phylogeny and network structure. Looking at the interaction pattern itself, Jordano used examples of plant-animal mutualisms to show how the overall interaction pattern depicted in the network appears more influenced by

Franck Jabot (Center for Disease Control & Prevention) the plant phylogeny, suggesting that the plant assemblage drives the interaction. Hence, coevolved trends might depend on resource tracking by animals, so that each plant species 'filters out' subsets of mutualists given species-specific traits that constrain their interaction through trait matching and trait convergence. The overall network of interaction has a distinct signal marked by the plants phylogenetic history. These patterns suggest both precise ways on how coevolution goes on beyond simple pairwise interactions and scales up to whole communities. Network thinking applied to plant-animal mutualisms is helping us to understand the complex patterns of interactions involved in their evolution.

Applying theories of arms races of plants and their parasites: Camellia-weevil system and rice blast disease
Akira Sasaki (Sokendai University)

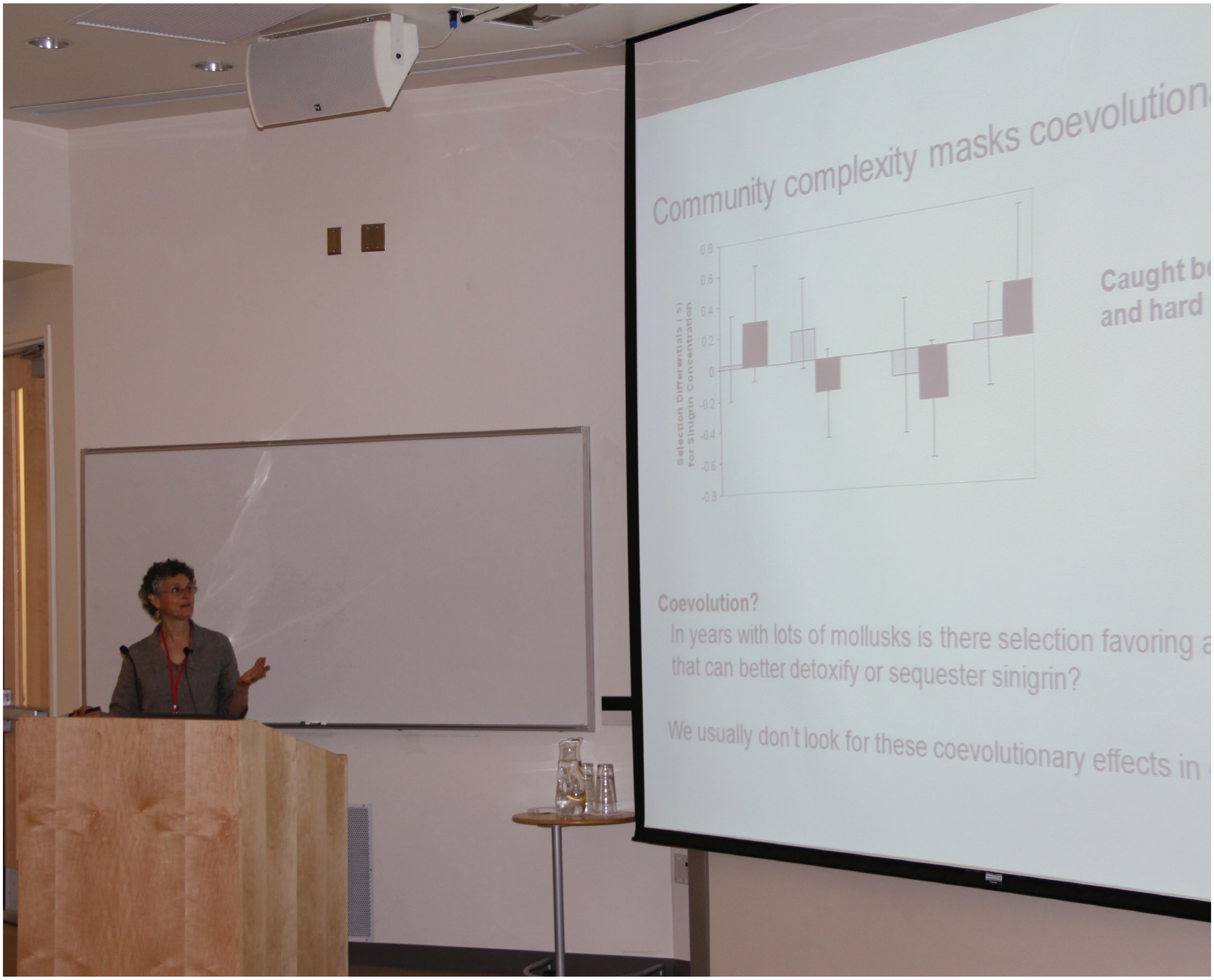
Sasaki talked about an eco-evolutionary model for the arms race of interacting quantitative traits, a defensive measure of host/prey and a countermeasure of parasite/predator, which he applied to the correlated geographical clines of Japanese camellia and its facultative seed predator, camellia weevil. Both the thickness of the fruit wall of plants to protect seeds and the length of the mouthpart of weevil used to bore through the wall for oviposition co-varied latitudinally over the populations where both camellia and camellia weevils are found. Coevolutionary outcomes are characterized by host productivity and the nonlinear cost for weevil mouthpart length. Sasaki introduced a mathematical model for the coevolution of parasite virulence and host resistance under a multilocus gene-for-gene interaction (Sasaki 2000, PRSLB). The degrees of parasite virulence and host resistance show coevolutionary cycles for sufficiently small costs of virulence and resistance. If either the cost of virulence or the number of resistance loci is larger than a threshold, the host maintains the static polymorphism of singly (or doubly or more, depending on the cost of resistance) resistant genotypes and the parasite remains universally avirulent. The theory is applied to the 40 years race of frequency changes of rice blast disease pathogen in response to the changes in the planting areas of resistant cultivars in Niigata prefecture, Japan. He proposed a model for accurately forecasting the race frequencies.

Community genetics of foundation forest trees as drivers of community diversity, structure, stability, and evolution
Thomas G. Whitham (Northern Arizona University)

The community phenotypes and genetic structure of foundation species are especially important to quantify as these species are by definition, "community and ecosystem drivers". Using observational and experimental studies of Populus and Pinus, Whitham's findings show that different tree genotypes support different communities of organisms (soil microbes, mycorrhizae, arthropods, vertebrates, understory plants, lichens, and pathogens) and these differences can be quantified as heritable plant traits. Thus, genetic diversity in foundation tree species affects biodiversity and is very important to conserve even when these trees are common on the landscape. Using diverse examples, the community phenotypes of forest trees can be traced from the individuals possessing the trait, to the community, and to ecosystem processes such as leaf litter decomposition and nitrogen mineralization, which in turn can feed back to affect the fitness of the individual expressing the trait. Based on the concepts of community phenotype, community heritability, community feedbacks, and foundation species, Whitham's work addressed issues such as: 1) How many genes in a foundation species does it take to produce a community phenotype? 2) How important are the community phenotypes of transgenic species and should they be included in the evaluation process of crops that will soon account for over 200 million hectares? 3) How do communities associated with a foundation species interact (e.g., soil microbes and canopy arthropods) to affect the fitness of individual genotypes of a foundation species? 4) How many foundation species does a community have and how do their interactions predictably affect the rest of the community? 5) Since most species in a community are rare, do they individually or cumulatively play an important role in driving the community or are they tag-alongs that are defined by the interactions of foundation species? 6) Is coevolution among relatively few foundation species the driver of community evolution? 7) How will climate change affect the interactions of foundation species and the evolutionary trajectories of communities? 8) How can a community genetics perspective contribute to the controversial issue of assisted migration? 9) Are emergent properties such as biodiversity and stability under genetic control and thus subject to natural selection? The answers to these questions have both basic and applied value, and have the potential to expand our knowledge of how complex communities and ecosystems evolve and function.

Evolution of virulence and mixed infections
Jacqui Shykoff (CNRS and Universite Paris Sud)

Shykoff noted that one very robust result of models of host-parasite co-evolution is that under regimes of mixed infection, where different strains of parasites compete for limiting host resources, parasites should evolve higher virulence strategies. This has wide reaching ramifications for optimal parasite strategies, since parasites are seldom alone in exploiting hosts. However, not all interactions between parasite strains within hosts are equal. When closely related parasite strains share hosts one might expect different evolutionary outcomes than


Community complexity masks coevolution

Caught b

and hard

Coevolution?

In years with lots of mollusks is there selection favoring a

that can better detoxify or sequester sinigrin?

We usually don't look for these coevolutionary effects in

when distantly related strains interact, particularly if the degree of relatedness between strains varies in nature such that parasites may be confronted with more or less related competitors. In addition to variation in the relatedness between interacting or competing parasite strains within hosts, the nature of the within-host interaction can vary greatly. Three types of within-host interactions have been identified, though this may not represent the whole range of the possibilities: competition for limiting host resources, production of public goods such as extra-cellular enzymes that promote infection success or efficient exploitation of the host and that can be used by all parasites within the same host, and spiteful interference between pathogen strains. Theoretical expectations differ for how virulence will change between single and mixed infections, and particularly for mixed infections of differing degree of relatedness between the parasite strains for these different types of interactions. Shykoff discussed the outcome of experiments designed to examine how virulence differs among mixed infections that vary in degree of relatedness in the anther smut fungus Microbotryum violaceum, a Basidiomycete fungal pathogen of plants that is transmitted by insect vectors, with a small aside to examine the idea of relatedness and the applications of kin selection to microbial interactions. Individual strains, when involved in mixed infections, drew greater resources from their host plant and produced more spores per flower than did strains that infected on their own. Furthermore, virulence (measured in terms of the degree of sterilization of the host plant) varied among mixed infections that differed in genetic relatedness among strains. Individual strains interfered with each other's ability to colonize the plant, thereby reducing the virulence of mixed infections for this trait, but interfered less when strains were closely related, suggesting spiteful interactions. Thus, for different traits of the infection, genetic relatedness among interacting parasite strains differentially influence virulence.

THURSDAY, APRIL 7

The consequences of exploitation for plant-pollinator mutualisms
Emily Jones (Washington State University)

Jones discussed how coevolution shapes the interactions between the coevolving species, rather than the more-commonly treated inverse problem. In a general plant/pollinator interaction, there are several possible exploiters that can impact the strength of coevolution, by reducing the attractive-

ness of the plant to the pollinator or vice versa, most simply by predation: seed predators that prey on the plant, or ambush predators that will capture pollinators visiting the flower. Jones describes a case well-established in the literature where exploiter-ants alter the fitness optimum of flowers to be more “closed”, which protects against exploitation but also makes the flower less accessible, and thus less beneficial, to the mutualistic pollinator.

In the balance of the talk, she describes first ambush predation by crab spiders, and second, seed predation by yucca moths. Based on the models she has developed, she shows predictions for qualitatively different outcomes (including, for example, extinction) depending on the model parameters. In particular, the relative rate of adaptation between the mutualistic organisms is crucial, and the presence of exploiter organisms can lead to coevolution between traits which do not directly interact. These predictions are consistent with the available empirical data in these two systems.

Reciprocal adapations as a key factor in the stabilization of a defensive ant-plant mutualism
Martin Heil (CINVESTAV, Mexico)

Heil talked about ant-plants which are important structural elements in many disturbed tropical ecosystems. The mutualism between plants and their defending ant symbionts is increasingly being used as a model to study general factors that stabilize horizontally transmitted mutualisms. Such mutualisms must be re-established each consecutive generation, and as a result, they are particularly prone to destabilization by cheaters (former mutualists) or parasites (non-reciprocating exploiters with no evolutionary history as a mutualist). Theoretical models predict high exploitation rates for high-reward mutualisms. Heil and collaborators empirically tested this prediction and found that sympatric Mexican Acacia myrmecophytes differ at the species level in the amount of food rewards and nesting space that they provide to their defending Pseudomyrmex ant mutualists. Several biochemical specializations help to exclude non-adapted potential consumers from feeding on the host-plant derived food rewards: food bodies and extrafloral nectar are biochemically protected from nectar-infecting microorganisms, nectar robbers, and herbivores. Interestingly, the same adaptations appear to make the symbiotic ants fully dependent on these rewards. At the phenotypic level, hosts that produced more extrafloral nectar were more aggressively defended by their inhabitants. Genetically fixed, species-specific plant traits combine with phenotypic plasticity to create ‘host sanction’ mechanisms, which bind fitness-relevant traits of both partners to each other. This assumption is confirmed by the observation that two high-reward producing species among four investigated host species were less commonly exploited by non-defending ant species. As reward production can be costly, this allows the diversification into 'low cost-high risk' versus 'high cost-low risk' strategies, and both strategies are indeed realized by sympatric and congeneric host species.

The Coevolution of Competitors in a Community Context
Peter Abrams (University of Toronto)

Abrams presented an extension of simple two-component systems of co-evolution (e.g. a single predator and a single prey species, or a single pair of symbiotes) to larger communities of multiple organisms. However, as the closing speaker of the session, he begins by providing a broad context on the field, with considerable humility and some humor.

First, he presents a very general definition of what should be considered 'coevolution', emphasizing that the definition should be general enough to include any mutual dependence on the distribution of different traits between or within populations. Many different types of traits can be subject to coevolution, under this very broad definition, and Abrams asserts that theory should encompass all of the phenomena he describes, which is not, he asserts, the state of the field. For example, phenotypic plasticity and behavior are generally treated as entirely distinct fields. Abrams gives specific models as examples, and shows that behavioral and community ecology models share many fundamental features in common, for example in a specific three-species system where only the "middle species" evolves. He also discusses fishery examples which do not seem consistent with existing models.

In a review of the literature, Abrams reports that the similarity between these phenomena is often not appreciated. Abrams emphasizes the need for novel approaches to simultaneously treat rapid evolution (including behavioral changes) and relatively slow evolutionary processes. He emphasizes that behavioral diversity can have unexpected evolutionary effects, including for example co-existence of species in similar niches, which is a major explanatory challenge given most current theory.

Following this literature review, he presents the work described in his abstract. As a simple model with more than two species, he presents a one-consumer two-resource model. Depending on the assumptions and terminological considerations, this system may or may not be subject to 'coevolution'. This model was extended to two consumers some time ago, predicting trait displacement between two competing consumers (i.e., each consumer will specialize in a different resource). However, empirical results in Stickelbacks, optimized to eat either plankton or insects based on the length of their gill-rakers, are not readily consistent with this result. This is another expression of the concave selection discussed by Hohenlohe: the organisms appear to be remote from the theoretical fitness maximum. This may be a result of rapid gene flow between populations presenting speciatiation/branching, which would result in overall population movement towards being a generalist when one resource or another is overharvested. In the closing discussion, he points out that a change in behavior does not have to be learned in the human sense; a similar rapid-evolution property can be observed in an entirely genetically programmed shift in behavior in response to environment, as long as that shift is not immediate.

Panel Discussion

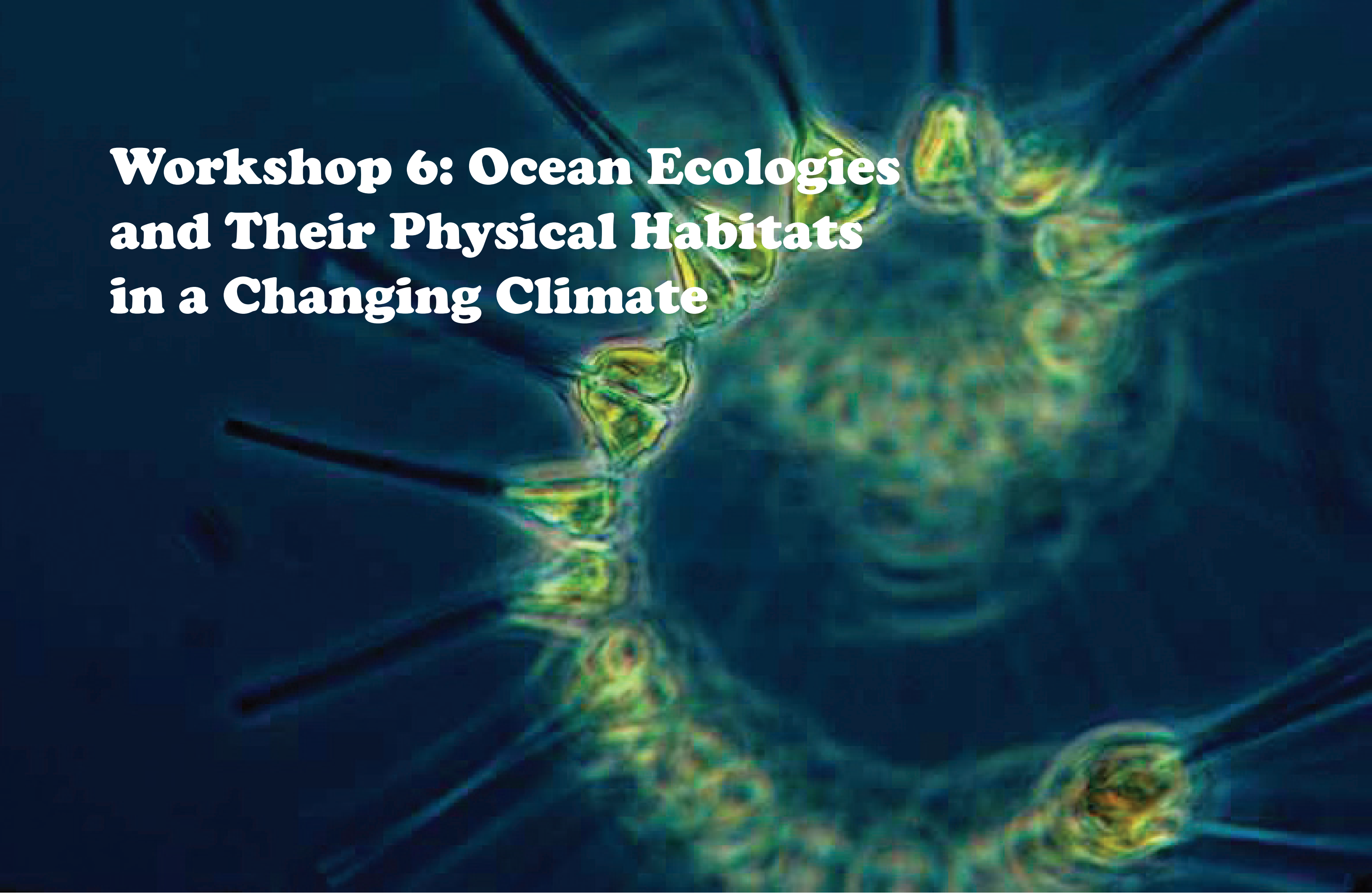
The panel discussion focused on the theme "Big ideas, big patterns, and big gaps." In particular, the group discussed three main points:

1) What are the main goals and common concerns? One big concern was that different definitions of coevolution came up during the workshop and it wasn't clear that everyone was talking about the same thing. Is everyone concerned about one single problem (coevolution) or is it just one specific outcome of a more general phenomenon, the interplay between ecology and evolution within community contexts? It was brought up that more attention could be paid to definitions, scales, scopes of interface, genetic basis of traits, alternative and null hypotheses, etc. Another big question is why study coevolution? Some answers brought up were to study diseases and to predict disease outcomes.

2) There exists a theory/modeling disconnect so we need to identify common research angles. In terms of coevolution, there needs to be more use of models to generate field studies, and field studies that generate models. Are we interested in studying coevolution as a phenomenon or as a mechanism? The general consensus is that it's both. It seems like the common connection is in the assumptions of models, not the mathematical analysis. One can test whether the assumptions are realistic based on empirical data, which will yield a more accurate model description and the right set of hypotheses to test. More broadly, the important question we should be asking is "where does coevolution help us to explain the natural world and the way it is?" For example, does it help us to explain trait distribution or community structure, and how?

3) How can we most profitably study the community context of coevolution. We have begun capturing more of the natural complexity that is the background and driving force underlying coevolution. What is the range of useful empirical and theoretical approaches? What are their respective benefits and drawbacks? It was pointed out that there has been a lot of modeling work done on food webs that would be natural to use to study the community context of coevolution. A particular challenge is how to describe networks/communities that lie in between very simple systems (that can be analyzed from the bottom up) and very complex systems (that can be analyzed from the top down), such as 4 or 5 species models.

Workshop 6: Ocean Ecologies and Their Physical Habitats in a Changing Climate



JUNE 20-JULY 1, 2011

Organizers: Ken Golden (University of Utah), Chris Jones (University of North Carolina at Chapel Hill), Hans Kaper (Georgetown), Mary Lou Zeeman (Bowdoin)

Report written by Rebecca Tien, Richard Gejji, and Juan Gutierrez

SUMMARY

The goal of the workshop was to bring together scientists from the mathematical, biological and geosciences to (1) identify phenomena in ocean ecology that might be affected by a changing global climate, and (2) discuss possible approaches to study these phenomena through mathematical modeling and analysis. Understanding the interplay between ocean systems and their biogeochemical environment is important for the carbon cycle and marine biodiversity. The workshop focused on two main themes: (1) Polar and sea ice ecologies, and (2) Phytoplankton and the carbon cycle.

The program of this two-week workshop consisted of tutorial lectures by experts (Week 1) and technical presentations by the participants (Week 2). The afternoons of Week 1 were used for group projects designed by the tutorial speakers. Summaries of the tutorials and technical presentations are given on the following pages.

During the workshop, several periods were set aside for interactive discussions. These discussions are summarized at the end of this report.

WEEK 1 TUTORIALS

MONDAY, JUNE 20

Factors Controlling Plankton Ecology
David Thomas (Marine Research Center, Finnish Environment Institute)

Dr. Thomas introduced sea ice biology and ecology with a focus on phytoplankton blooms and marine production controls. Topics such as the balance between respiration and photosynthesis, the relationship between photosynthetic rate and irradiance, and critical depth theory were explored.

Ecological Modeling
Alan Hastings (University of California)

Dr. Hastings talked about predator-prey dynamics with applications to phytoplankton and upwelling models. Equilibrium stability analysis, the generation of periodic orbits, and the importance of appropriate model choice were discussed. Connections to classic ecological experiments were made.

TUESDAY, JUNE 21

Biology/Physics Interface in Sea Ice
Steve Ackley (University of Texas)

Dr. Ackley discussed properties of Antarctic sea ice and how they have changed over the past several years. The importance of brine pockets as food storage for phytoplankton was explained. Sea ice formation, depletion and nutrient exchange were discussed. The cycle of polar algae and sea ice dynamics were also introduced and explained.

Sea Ice Structure and Processes
Ken Golden (Mathematics, University of Utah)

Dr. Golden spoke about sea ice structures and processes that will improve our understanding and projections of climate change. Sea ice covers 7 to 10% of Earth's ocean surface, is a boundary between ocean and atmosphere, and is an indicator and agent of climate change. Brine expulsion from sea ice formation results in water beneath the ice becoming cooler and saltier; this denser water sinks rapidly to great depths and this drives circulation in the world's oceans. Polar ice caps are critical to global climate in reflecting incoming solar radiation. Sea ice is a porous composite; fluid flow through porous sea ice mediates key processes in polar climate and ecosystems.

A Glacier Paleoclimate Perspective for the Last 10,000 Years
Lonnie Thompson (Byrd Polar Research Center, The Ohio State University)

Dr. Thompson gave a general overview of mechanisms influencing climate. We tend to think locally, but the impact of our actions is global. He illustrated his remarks with observations from the Quelccaya Ice Cap in Peru, which is the largest glaciated area in the tropics.

WEDNESDAY, JUNE 22

Oceans: Dynamics, Transport/Mixing and Climate Change
Emily Shuckburgh (Natural Environmental Research Council, British Antarctic Survey)

Dr. Shuckburgh explained the dynamics of the ocean circulation and discussed the equipment used in arctic exploration (ships, submarines, labs, etc.) in the context of studies in the Antarctic region. Several aspects of ocean surface and sub-surface circulation patterns were presented. Examples of rotating fluid dynamics were presented, along with their respective mathematical formulation. The effects of climate change were discussed.

Excursion to the Byrd Polar Research Center

Ken Golden (University of Utah)

THURSDAY, JUNE 23, 2011

Air-Sea Carbon Dioxide Exchange
Nicole Lovenduski (Institute of Arctic and Alpine Research, University of Colorado)

Lovenduski focused on the critical role that the ocean plays in the global carbon cycle. Outside of carbon sequestration by terrestrial plants, the ocean is the major sink of atmospheric carbon. CO2 is special, because it reacts with water to form bicarbonate and carbonate ions; the reaction reduces the concentration of dissolved CO2 in the ocean, allowing for continued CO2 uptake from the atmosphere. The air-sea flux of CO2 is controlled by the difference between the atmospheric and oceanic pCO2. (pCO2 : partial CO2 pressure.) The oceanic pCO2 depends on temperature, alkalinity, dissolved inorganic carbon (DIC), and salinity; the partial pressure of a gas above a liquid is directly proportional to the concentration in the liquid (concentration = partial pressure times solubility). In the ocean, the solubility component is determined by the temperature and salinity, and the concentration is determined by the alkalinity and DIC. Given that temperature affects solubility, an important question is how a warming of the oceans might impact the flux of CO2. Although temperature can have a significant impact on increasing pCO2, it is not the only relevant factor. As mentioned earlier, pCO2 in the ocean is a function not only of temperature but also of DIC, alkalinity, and salinity. In oceanic biogeochemistry, the cycling of carbon from the surface waters to the ocean interior is known as the biological pump. Most of the carbon that reaches the ocean depths is a result of sinking organic matter. The formation of organic matter tends to decrease DIC but increase alkalinity, which can lead to a decrease of pCO2. The formation of calcium carbonate from CO2 can have the opposite effect on CO2.

Modelling Biogenic Gas Concentrations and Fluxes in Sea Ice: Wishful Thinking?
Jean-Louis Tisot (Earth and Environmental Sciences, Université Libre de Bruxelles)

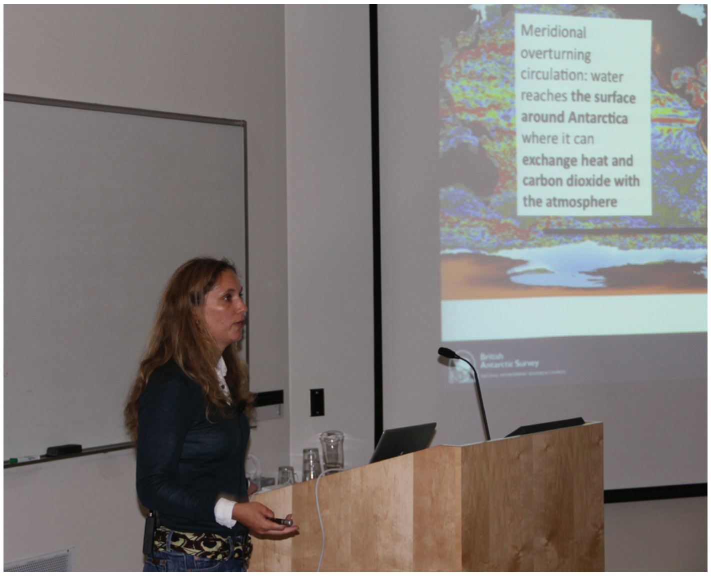
Dr. Tisot first discussed the importance of sea ice. Despite the fact that sea ice covers a large portion of the Earth's surface, its role in the global carbon cycle is little understood. An important question is whether ice is permeable or impermeable to gas exchange between ocean and atmosphere. Indeed, what he has seen is that exchange is limited to the leads between ice floes in winter, but throughout the rest of the year there are several mechanisms through which gas exchange can occur. In general, the properties of the gas (i.e., particular types of gases present) play a key role in permeability of sea ice. Gas content and composition are dictated by a number of different processes. Any model should include: initial entrapment of gases in the ice, internal physical/biogeochemical transformations, internal transport, fluxes between ice and atmosphere. The next step is to run sensitivity analysis.

The second part of the talk looked specifically at work both in the Arctic and the Antarctic. In an ISPOL cruise, both CO2 fluxes (to determine whether the ice was permeable) and pCO2 gradients were examined. The second example was from a SIMBA cruise. In summary, Dr. Tisot pointed out the complicated nature of diffusion through the ice and gas exchange between the ice and the atmosphere. Major conclusions are: sea ice is not a passive impermeable layer but contributes actively to the exchange of various climatically important gases between the ice and the atmosphere; there have been many recent advances in understanding the gas composition of sea ice and the processes that govern it; both biological and physicochemical processes govern the gas concentrations that drive flux; and finally, the complexity of the system poses large problems for modeling.

FRIDAY, JUNE 24, 2011

The Role, Growth, and Fate of Phytoplankton in the Southern Ocean: Observations, Models, and New Approaches to Old Problems
Walker Smith (Virginia Institute of Marine Science, The College of William and Mary)

Dr. Walker discussed the role of phytoplankton in the Southern Ocean, particularly in the Ross Sea. He started off the talk by giving an outline of the annual climatology of phytoplankton growth. Abundance is initiated in early November as ice starts to melt and reaches a maximum in late December. The biomass maximum is limited by iron availability. The dominant species is colonial haptophyte Phaeocystis Antarctica. After this point, P. antarctica disappears rapidly and the assemblage is then dominated by diatoms, particularly near ice edges. Ice advance is once again initiated in late February and phytoplankton growth stops at this point. During some years, this pattern of a single annual bloom is replaced by a bimodal pattern where a second bloom occurs that is dominated by diatoms. This raises two questions: Why does this second bloom occur, and why the diatom dominance? It is possible that the secondary bloom is caused by iron inputs, but it is unclear where these iron inputs might come from. Other recent findings have also shown that the region exhibits both temporal and spatial variation. This heterogeneity is assumed to be a result of oceanographic processes. Modeling attempts have so far failed to capture the variability of phytoplankton growth in the region. Models of circulation and biogeochemical processes however do exist and can be used to compare in situ observations. Another approach to understanding the system is the use of newly available technologies (gliders, autonomous vehicles, etc.), which are cost-effective and can give insight into oceanographic events and biogeochemical cycles.



Emily Shuckburgh (British Antarctic Survey)

Dynamics of Phytoplankton-Nutrient Interaction
Arjen Doelman (Mathematisch Instituut, Leiden University)

The talk was broken into three parts: 1. The dependence of phytoplankton on light (self-shadowing as a non-local effect, mathematics of blooming); 2. Phytoplankton-nutrient interactions and the Phytoplankton Paradox (due to Hutchingson), which states that numerous species can coexist on what appear to be a limited array of resources; 3. The simplest PDE model for phytoplankton-nutrient-light interactions and numerical simulations in MATLAB to study the onset of phytoplankton blooms and pattern formation of blooms.

WEEK 2 TECHNICAL PRESENTATIONS

MONDAY, JUNE 27, 2011

Climate Change and Critical Behavior of Sea Ice
Ken Golden (University of Utah)

As sea ice melts and forms melt ponds, brine flows through the sea ice due to increased permeability. Evidence was provided that sea ice floes have self-similar structure and thus can be understood using percolation theory. Dr. Golden then showed a correspondence between theoretical and experimental results on the critical behavior that sea ice can display, developed the idea for spectral up-scaling for sea ice structures, and showed how the processes of snow-ice formation and melt pond evolution can be monitored electromagnetically.

CO2 Dynamics and Related Air-Ice Exchanges in Sea Ice
Bruno Delille (Universite de Liege)

Dr. Delille gave a historical overview of CO2 measuring and analysis techniques and discussed the ocean's role as a sink and sea ice's seasonal role as a transient source, then as a sink, for CO2. The role of temperature and salinity, precipitation/dissolution of CaCO3, and primary production in the dynamics of CO2 was analyzed.

Paleo-perspective of the Development of Sea Ice and Related Biota in the Arctic Ocean
Leonid Polyak (Byrd Polar Research Center, Ohio State University)

In the past several decades, the Arctic environment has experienced an increase in average temperature and a decrease of both the extent and the volume of sea ice. This talk provided a perspective on how the recent changes in the Arctic environment compare to changes experienced over long time scales. In particular, low ice conditions currently projected are likely to have paleo-analogs that existed during past major warm intervals. Implications of the changing Arctic environment on sea ice and Arctic Ocean biota were presented.

An Energy-Budget Framework to Address Polar-Bear Population Viability in a Changing Climate
Peter K. Molnar (Princeton University)

As global climate change occurs, polar bears face a variety of threats due to reduced access to prey, including starvation, smaller litter size and mortality. In this talk, Dr. Molnar introduced a Dynamic Energy Budget (DEB) model, showed that model predictions for mass and litter size are consistent with experimental observations, and provided predictions for polar bear fitness under starvation conditions. He plans to extend the model to include other species and indicated that such models can be used for risk assessment.

TUESDAY, JUNE 28

Climate Change and Marine Ecosystems – From the Amazon to Antarctica
Patricia Yager (University of Georgia)

Climate change impacts and is impacted by ocean ecosystems. Some species have grown while others have been depleted as climate change occurs. In particular, the effectiveness of the biological carbon pump influences and is influenced by temperature changes and community structure. Dr. Yager indicated that understanding emergent phenomena that arise from these global connections could benefit from complex systems theory.

Phytoplankton Growth in Oligotrophic Oceans: Linear theory
Antonios Zagaris (University of Twente)

Dr. Zagaris discussed a PDE model of two reaction-advection-diffusion equations describing the evolution of plankton and nutrient concentrations. Non-dimensionalization, scaling, and linear stability analysis were explored. The inclusion of light attenuation in the model allowed for the emergence of two distinct localized patterns corresponding to benthic layers, where plankton localizes close to the bottom, and deep-chlorophyll maxima, where plankton is localized in a region inside the water column.

Rebecca Tien (MBI)

Phytoplankton Growth in Oligotrophic Oceans: Weakly Nonlinear Theory
Arjen Doelman (Mathematisch Instituut, Leiden University)

Dr. Doelman presented the problem of bifurcating DCMs under nutrient-light co-limitation from a weakly nonlinear point of view. Particularly, he presented the problem of existence of an infinite number of eigenvalues tightly clustered around the origin. Explicit asymptotic results were presented, valid both close to and far from the bifurcation point, verifying the stability of the bifurcating DCM.

Evolution of Phytoplankton Cell Size in a Variable Environment
Ariane Verdy (University of California, Los Angeles)

Dr. Verdy discussed organization of phytoplankton communities along a latitudinal gradient in nutrient supply, sea surface temperature, and insolation. The size of phytoplankton cells determines their competitive ability, sinking rate, and potential to export carbon to the deep ocean. Dr. Verdy presented allometric models for the evolution of phytoplankton cell size to explain that small phytoplankton species dominate the equatorial and subtropical oceans while larger species are more abundant in sub-polar regions. The model shows that increasing body size can be a successful adaptation, even in the absence of temporal variability or predation.

WEDNESDAY, JUNE 29

Sea Ice and the Biogeochemical Cycle
Martin Vancoppenolle (Université Catholique de Louvain, Louvain-la-Neuve, Belgium)

Dr. Vancoppenolle explained how biogeochemistry in sea ice is coupled with liquid brine dynamics. Future projections of the polar oceans are subject to some of the largest uncertainties. Among the sources of uncertainty is the role of sea ice: Earth system models consider sea ice as biologically inert, while observations indicate active biogeochemistry in sea ice. The fact that sea ice is so prone to microbial life is due to the fact that sea ice can be viewed as a matrix of solid ice with liquid inclusions of brine. Depending on permeability, brine inclusions are connected or not with the underlying ocean. The brine network is ventilated by brine drainage mechanisms, supplying or flushing out nutrients.

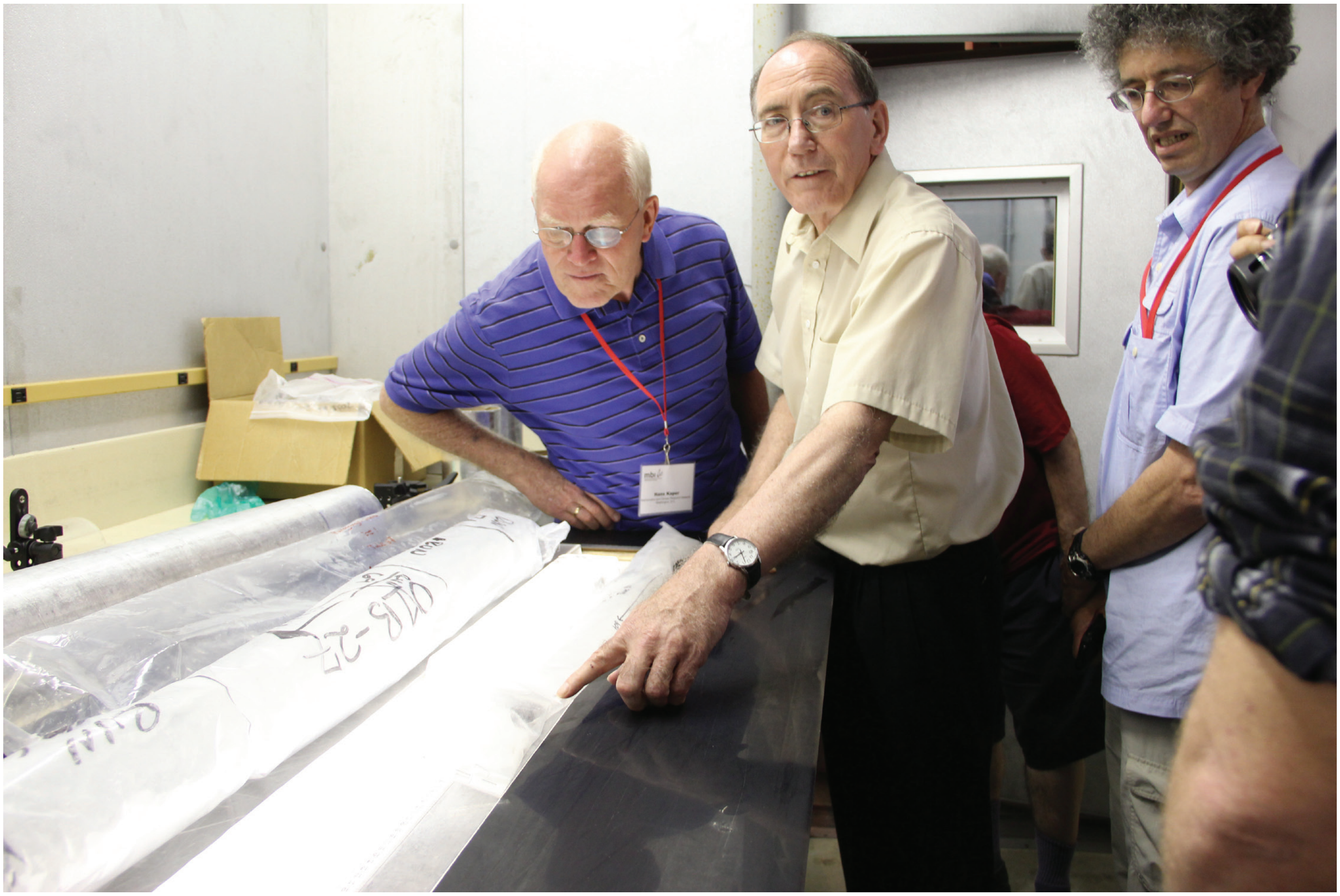
Predicting the Behavior of Ocean Ecology in a Changing Climate: from simple theory to global climate models
Irina Marinov (University of Pennsylvania)

Dr. Marinov proposed from theoretical arguments a "critical nutrient hypothesis" stating that, in the low-nutrient regions, future nutrient decreases due to increasing stratification will affect smaller phytoplankton biomass than diatoms, with consequences for export production and the carbon cycle. The opposite behavior is expected in the high-nutrient high latitudes, with future nutrient decreases affecting more diatoms than small phytoplankton. Dr Marinov proposed an analytical framework linking changes in nutrients, light and temperature with changes in phytoplankton

THURSDAY, JUNE 30

Modeling of Microbial Biofilms and Mats
Isaac Klapper (Montana State University)

Dr. Klapper first gave a general background on biofilms and discussed the standard questions (productivity, tolerance, community structure). Next, he went into some specific examples of different biofilms, mat formation, structure and ecology. He discussed the difficulty in growing complex biofilm communities in labs because they have rather complex community structure (e.g., they rely on each other for nutrients in ways that are hard to tease apart). The last two sections of the talk focused more specifically on compartmentalized biofilm models. He talked about simple box models, which can be used for things like pore channels in ice river and shelf systems, and more complex models. In a simple model, food diffuses into film from above, is consumed and fuels growth, and as a consequence the biofilm grows out and upwards. He moved on to talk about multiple substrates containing multiple species, which mathematically is a moving boundary problem that is solved with a system of one-dimensional PDEs. The final portion of the talk covered the physics and chemistry of biofilms and the components that go into this type of model, including the microbiology factors (growth, ecology, metabolics) as well as the physical and chemical properties. He



Hans Kaper, Lonnie Thompson, and Alan Hastings observe glacial ice at the Byrd Polar Research Center.

also discussed some experimental approaches to investigate the physical and chemical properties of biofilm growth and structure.

The Decline of Calanus finmarchicus in the Gulf of Maine: Using Modeling to Investigate the Relative Role of Top-down Verses Bottom-up Processes
Rebecca Tien (MBI, The Ohio State University)

This talk focused on a regime ecosystem shift in the Gulf of Maine, which occurred in the 1990s and led to increases in most zooplankton species, including the early stages of Calanus finmarchicus, but a paradoxical decrease in the later stages of C. finmarchicus. Simple ODE models were used to look at the impact that changes in phytoplankton abundance (bottom-up) and increases in herring abundance (top-down) might have simultaneously played in structuring the C. finmarchicus throughout this decade. A series of different models were suggested and some optimization techniques were discussed.

The Grand Unified Theory of Copepods
Nicholas Record (Gulf of Maine Research Institute)

This research is motivated by the question how copepods will respond to global warming. Other motivating questions include community structure (size, diversity, etc.) and why some species of copepods dominate in one region and different species in another. After a general overview of copepod ecology, the speaker discussed his approach to modeling copepods on a "macro-ecological" level. The ecology of copepods is dominated by oceanic mesozooplankton; they are the most abundant metazoan in the world, which makes them important grazers on the annual spring bloom and a crucial group of organisms for transferring primary production to higher trophic levels; they have a complex life cycle, which can include periods of dormancy lasting for many months and lead to generational pulses. The most common simple copepod ecology models ignore the fact that zooplankton spans many trophic levels, come in all sizes (ranging from microns to meters) and include 12 phyla. The speaker uses the Navier-Stokes equations of fluid dynamics and a generic description of copepods so the model can be applied to a multitude of different copepod species. For each species, the model can specify a variety of individualized parameters such as temperature-dependent development rate, search volume, handling time, method of spawning, and so on.

FRIDAY, JULY 1

The Role of Sea Ice in Past Climate Cycles
Raj Saha (University of North Carolina, Chapel Hill)

Dr. Saha began with a brief background on glacial-interglacial cycles (each lasting approximately 100,000 years) over the last 1 million years. These cycles are characterized by abrupt

warming and slow cooling, which is related to how quickly ice sheets recede and how slowly they build back up in size and volume. His study focuses on the last cycle, using data from Greenland ice cores. Within this cycle, individual warming events occur with regular frequency (about once every 1500 years). He discussed several hypotheses that have been proposed to explain the origin of these periodic fluctuations and the strengths and weaknesses of each. The goals of his research are to look at the mechanisms that are responsible for the abrupt climatic fluctuations and the robust 1500-year periodicity. His model focuses particularly on the North Atlantic, and he addressed the various climatic components of the glacial N. Atlantic including physical features (e.g., land ice) and circulation and precipitation patterns.

Simulating Ocean Ecosystems in a Changing Climate with CESM-(BGC): Potential Intersections with Math
Keith Lindsay (Climate and Global Dynamics Division, National Center for Atmospheric Research, NCAR)

The Community Earth Systems Model (CESM) is a coupled climate model that includes components for the Earth's atmosphere, ocean, land, and sea ice and can include additional information on carbon cycles, atmospheric chemistry and land ice. Dr. Lindsay discussed the details of the model as well as some of the many challenges in dealing with a model that incorporates multiple processes and multiple organisms. The last portion of his talk covered various applications of CESM. Examples given included using CESM to prescribe fossil fuel emissions and running CESM to determine the atmospheric CO2 content in the 21st century under various "what-if" scenarios).

SUMMARY OF DISCUSSION SESSIONS

Throughout the workshop, several sessions were set aside for interactive discussions. Topics for these discussions were solicited during and after the presentations and collected in a list on the whiteboard in the front of the auditorium.

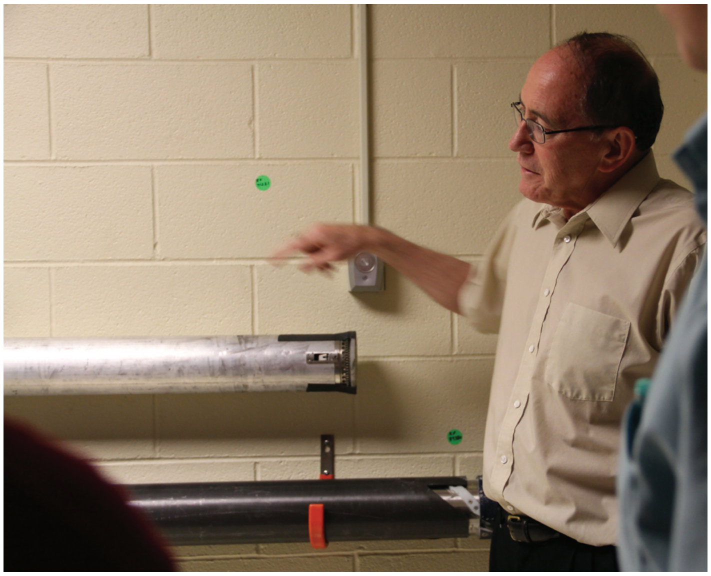
The final session of Week 1 was devoted to the formulation of a set of research questions, discussion topics for Week 2, and potential tutorial topics.

Research questions - General

- Multi-scale methods in climate modeling
- Stochastic and hybrid modeling of small-scale processes
- Tracing effects of heterogeneity and uncertainty
- Develop intermediate complexity models to bridge the gap between conceptual dynamical models and realistic numerical models (Colin Reynolds, for fresh water systems). Example: introduce nonlinearity in linear models as alternative for parameterization
- Sensitivity of parameterization vs. physical mechanistic description
- Ideas for new experimental techniques

Research questions – Sea Ice

- Multi-scale modeling of sea ice (cf. Carbon change project)
- Global impact of tropics vs. poles on different time scales (Lonnie Thomas's comments)
- Salinity profile in sea ice, a fundamental small-sale process
- Process models for sea ice formation and melting (differences between Arctic and Antarctic regions); sensitivity of melting to process parameters
- Role of sea ice in gas exchange at atmosphere-sea ice interface
- Snow microstructure
- Dependence of permeability on crystalline structure of ice, role of snow, transition zone
- Interaction between physics and biology, feedback mechanisms and models. Example: drain holes and seals



Lonnie Thompson shows the drills that are used for glacial ice.

Research questions – Carbon Cycle

- Identify relevant scales, processes at each scale, and relevant questions in each context (CO2, primary production, melting)
- Develop a model of the biological pump
- Estimate total respiration of ocean from the spatial distribution of C13; compare northern and southern oceans
- Estimate strength of the biological pump from the difference in C13 between atmosphere (or lake sediment or ice core) and deep ocean
- What is the role of eddies in carbon sequestration?
- Transfer coefficient for ocean-atmosphere gas exchange (parameterization)

Research questions – Algal blooms

- Is there a separation of scales in copepod interactions? If so, can we apply Geometric Singular Perturbation Theory to achieve dimension reduction?
- Heteroclinic cycles in Doelman/Zagaris system
- Apply "community ecology theory" vs. "individual species theory"
- Ecosystem modeling of Southern Ocean (Katie Green, Global Ecosystem GLOBEC)
- Extending Emily Shockburgh's use of invariant manifolds to other types of critical points

Suggestions for Tutorial topics

- Reanalysis: What is it?
- Non-dimensionalization and scaling (Books by Mark Holmes, Fowler, Strogatz)
- What can we learn from biofilms for sea ice?
- How data is inferred from ice core/ocean sediments
- Translating dynamical systems theory for biology
- Ocean acidification
- Experimental design
- Model validation by "hindcasting" and forecasting

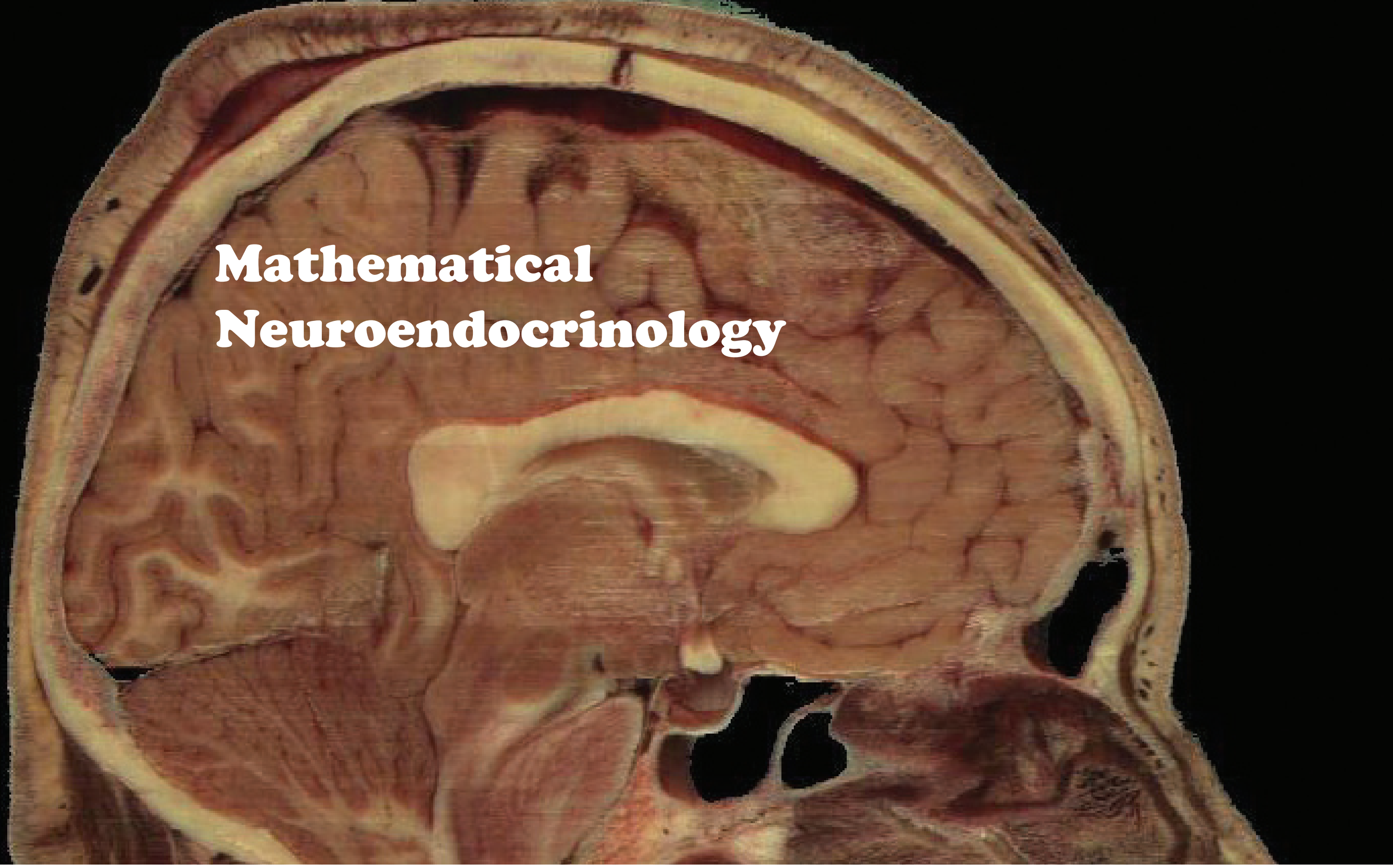
Topics for Further Thought

- What is the difference between evolution and competition [e.g., Darwin project] in the NPZ model in the context of general circulating models?
- How much biodiversity is enough for a global climate model to capture/forecast biogeochemistry?

Several participants enquired about the biological pump. Following is a summary of the discussion.

THE BIOLOGICAL PUMP

The biological pump is the mechanism for carbon sequestration that is driven by living organisms (phytoplankton) and mediated by the Earth's oceans (see Falkowski & Oliver, 2007). Atmospheric CO2 is taken up by phytoplankton in the upper ocean layers, becomes part of the food chain and either sinks to the ocean interior or is released back into the atmosphere. Modeling the biological pump is complicated because there are many players (about a dozen distinct functional groups of phytoplankton, depending on the desired level of detail) and the processes are not well understood. For example, the efficiency of the biological pump is strongly influenced by turbulent diffusion. At this point, it is not even known whether the biological pump is a source or a sink of carbon. Models could be box models, intermediate complexity models (remineralization models), NPZ, etc.



Mathematical Neuroendocrinology

AUGUST 9-13, 2010

Organizers: Richard Bertram (Florida State University), Arthur Sherman (LBM/NIDDK/NIH), Mary Lou Zeeman (Bowdoin College), Gareth Leng (University of Edinburgh), Stanko Stojilkovic (NICHD)

Report written by Marisa Eisenberg, Harsh Jain, and Deena Schmidt

OVERALL SUMMARY

This workshop was the second in a series of mathematical neuroendocrinology workshops (the first was held at AIM). The goals of this workshop were to foster collaborations between mathematicians and experimentalists, discuss problems in neuroendocrinology that can be addressed using mathematics, and highlight open problems and questions in neuroendocrinology to bring young mathematicians and experimentalists into the field. The workshop explored neuroendocrine regulation and function, including pituitary and hypothalamic control of the endocrine axes. Neurons in the hypothalamus drive or inhibit pituitary cells to secrete hormones which control endocrine glands (such as the thyroid, adrenals, ovaries, and testes) throughout the body. The complex interactions of these cells yield remarkable patterns including circadian and ultradian rhythms, and complex feedback systems. Mathematical neuroendocrinology uses mathematical modeling and analysis to understand these complex interactions and suggest new experiments.

MONDAY, AUGUST 9
TUTORIALS

Introduction to the Neuroendocrine System
Arturo Gonzalez-Iglesias (Florida State University)

Arturo opened the workshop with a tutorial introducing neuroendocrine biology. He began with the nervous system, followed by the endocrine and exocrine glands. He took us through the history of how hormonal regulatory systems were discovered, and introduced basic pituitary structure, function, and regulation. Next, he surveyed some of the common feedback control systems for hypothalamic and pituitary hormones, such as the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-thyroid (HPT), and prolactin (the so-called 'black sheep' of the endocrine system) regulatory axes. He introduced the idea of hypothalamic control of the anterior pituitary via the hypophysial portal system, and went over some of the hypothalamic nuclei (suprchiasmatic nucleus, paraventricular nucleus, etc.). He also explored several example axes in more detail and discussed the history of pituitary control and the localization of neurons producing hypothalamic control hormones (e.g. thyrotropin-releasing hormone from the paraventricular nucleus).

Introduction to the analysis of biomathematical models
Richard Bertram (Mathematics, Florida State University)

Bertram gave an introductory lecture on the basic principles and practice of biomodeling. He began by overviewing some of the typical goals of modeling in mathematical biology—

to integrate and interpret data, make testable predictions, design experiments, and find gaps in the common 'box and arrow' diagrams used for signaling pathways. He introduced two main classes of models: deterministic and stochastic. Next he discussed some of the difficulties involved in parameterizing biomodels. Because most parameters are typically not measurable, parameter estimation can be a challenge. He then progressed from linear to nonlinear ordinary differential equations (ODE's), to delay differential equations, introducing concepts of dimensionality, stable/unstable equilibria, bifurcations, phase portraits vs. time course, and nullclines, which he illustrated using the Morris-Lecar model. Next, he moved to stochastic models, introducing Monte Carlo simulation and Markov processes.

Breakout Sessions

After lunch, the participants brainstormed topics and split into several breakout sessions. Among the topics suggested were frequency sensitivity of pituitary gonadotrophs, dendritic hormone secretion, optimizing model complexity for different questions and scales, paracrine interactions, and many others. The group settled on two main topics: more math for biologists (a more detailed exploration of how to go from model equations to final results), and mathematics for embracing heterogeneity. Richard Bertram and Arthur Sherman agreed to head up the modeling tutorial for biologists. The 'more math for biologists' group covered more details on limit cycles and bifurcations, and agreed that a second session along these lines might be useful. The mathematics for heterogeneity group split into two subgroups as it was quite popular— the first subgroup explored how to distinguish between stochastic and deterministic behavior, and touched on the relationship between heterogeneity and stochasticity. They came up with several criteria for using a stochastic/deterministic model, although the choice is not always clear. The second group on heterogeneity discussed how to handle heterogeneity in vasopressin firing and secretion, which can happen at different time scales. They explored questions of: are there multiple mechanisms? Should we model these processes in the same way or not? The breakout sessions concluded with the participants rejoining in the auditorium and a brief wrap up by each group.

TUESDAY, AUGUST 10

Signaling Within and Between Pituitary Cells
Stanko Stojilkovic (PDN/NICHD/NIH, Bethesda, MD)

Stojilkovic's talk focused on the neuron-like behavior of endocrine pituitary cells in firing spontaneous action potentials mediated by voltage-gated sodium, calcium, potassium, and chloride channels. In particular, he used the example of pituitary lactotrophs to present the current state of knowledge on the complex relationship between electrical activity and calcium/cyclic nucleotide signaling. Numerous G protein-coupled receptors expressed in these cells stimulate or silence electrical activity, cyclic nucleotide signaling and action potential-dependent calcium influx and hormone release. These cells also express several subtypes of extracellular ligand-gated ion channels whose activation is linked to amplification of pacemaking activity and the facilitation of calcium influx and hormone release. The functioning of the ATP mediated P2X channels that help regulate this activity was discussed in detail and the precise role of sodium, calcium and cyclic AMP vis-à-vis these channels presented. A major question in this field is the identification of channels contributing to pacemaking depolarization. Dr. Stojilkovic presented exciting new work relating to this, which is soon to be published.

Modeling of Exocytosis in Endocrine and Neuroendocrine Cells
Arthur Sherman (LBM/NIDDK/NIH, Bethesda, MD)

Dr. Sherman presented a series of mathematical models designed to understand the precise mechanism by which secretory vesicles perform their function in response to calcium concentrations, and the affinity of this release mechanism for calcium, in beta cells. In particular, he sought to address the following hypothesis – in neurons, secretory vesicles are physically closely associated with calcium channels but not in endocrine cells, where a subset of vesicles distant from these channels may have enhanced sensitivity to calcium and play a larger role in insulin secretion. It is known that insulin secretion in response to glucose stimulation is biphasic in nature. To explain this, Dr. Sherman imposed a 2-compartment model to handle the temporal distribution of calcium. The first of these described the set of exocytotic reactions between insulin containing granules and the cell membrane, which uses the SNARE hypothesis (a mechanism for the specific docking and fusion of transport vesicles with their target membranes). This was assumed to occur only in the microdomain near voltage sensitive L-type calcium channels. In contrast, resupply and priming of granules were assumed to depend on cytosolic calcium, whose concentration was governed by four types of transporters. In this manner, the model could generate both the fast granule fusion and the slow insulin secretion found experimentally in response to a step of membrane potential. In order to reconcile this model with recent experimental observations that hint at the existence of two pools of releasable granules with differing calcium sensitivities, Dr. Sherman proposed an extension to his model by the addition of a highly calcium sensitive pool that resides mainly away from calcium channels. The new model was shown to be compatible with a multitude of experimental data from single cells on the highly calcium sensitive pool and from stimulation of islets of glucose under a variety of initial conditions.

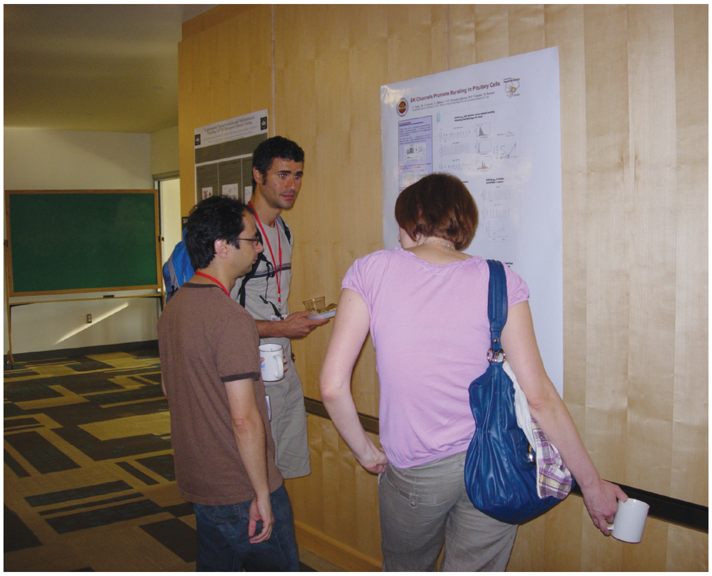
Breakout Sessions

The breakout sessions for the day were on circadian/sleep, metabolism/core clock, and paracrine interactions. After a break, a new set of sessions were announced, on mechanisms for bursting and time scales and interactions between oscillators. No group leaders were chosen, instead the groups got together for informal discussions relating to these topics.

WEDNESDAY, AUGUST 11

Intrinsic and extrinsic contributors to gonadotropin-releasing hormone (GnRH) neuronal activity
Sue Moenter (University of Virginia)

It is known that the release of gonadotropin-releasing hormone (GnRH) from nerve terminals in the hypothalamus occurs in an episodic fashion and it is critical for encoding downstream pituitary response and fertility. Episodic release likely arises from the intersection of several components including intrinsic properties that generate repeating activity, synaptic inputs and the network interactions that bring about synchrony of neuronal activity. However, despite their importance, the mechanisms underlying episodic GnRH release are not well understood. Moenter first talked about the synaptic regulation of GnRH neurons, and then presented preliminary work on how metabolic inputs that regulate fertility alter intrinsic properties of GnRH activity. In particular, GnRH neurons exhibit burst firing behavior, and such bursting appears to be intrinsic. She addressed fundamental questions such as what initiates a burst? What maintains, changes, or terminates a burst? Also, Moenter discussed a method developed by her graduate student, Kasia Glanowska, called Fast Scan Cyclic Voltammetry (FSCV) that electrochemically measures GnRH release in brain slices.



Viability of Autocrine Regulation in Synchronizing Diffusely Distributed Endocrine Neurons Producing Pulsatile Hormonal Signals
Yue-Xian Li (University of British Columbia)

Li gave the second talk of the morning. He began with introductory material about gonadotropin-releasing hormone (GnRH) neurons and their role in mammalian reproduction. In particular, he noted that reproduction in mammals is controlled by the pulsatile release of GnRH and that between 800 and 2000 GnRH neurons participate in the generation of GnRH pulses. Their cell bodies are distributed in a scattered manner in designated areas of the hypothalamus. Various experimental models have been developed and studied (including cultured hypothalamic tissues, placode-derived GnRH neurons, and GT1 cell lines); however a mechanistic explanation for the origin of GnRH pulsatility remains unknown. One major obstacle is identifying the mechanism for synchronizing scattered neurons. Li's talk was aimed at studying the feasibility of autocrine regulation in synchronizing GnRH neurons using mathematical models to describe diffusely distributed GnRH neurons in two-dimensional space. The models Li discussed are based on experiments (in GT1 cells and hypothalamic neurons in culture) showing that GnRH neurons express receptors that allow GnRH to regulate its own secretion through an autocrine effect. GnRH binding to its receptors triggers the activation of three types of G-proteins, two that activate and one that inhibits GnRH secretion, suggesting that GnRH secreted by GnRH neurons serve as a diffusive mediator as well as an autocrine regulator. Modifying a model based on LeBeau et al. (Fletcher and Li, 2009 Biophysical Journal), Li described an improved model of the autocrine mechanism in vitro that showed the robustness of the synchronization mechanism. He concluded that GnRH as a diffusive autocrine mediator is capable of synchronizing GnRH secretion between spatially distributed GnRH neurons. As a consequence of the fixed thresholds for activation of the three G-proteins, synchronized GnRH pulses only occur when the GnRH neurons are appropriately spaced, and this is one plausible explanation for why GnRH neurons are distributed in the hypothalamus in a scattered way. When nearest neighbor distance is fixed at appropriate values, synchrony only occurs within an appropriate range of the diffusion constant D. At certain low values of D, GnRH neurons isolated from each other maintains their own pulsatility. Synchrony also occurs in randomly distributed neurons when the average cell density is neither too high nor too low. Higher secretion rate helps broaden the domains of synchrony and pulsatility in both the diffusion constant and the distance between the two neurons.

Breakout Sessions

The breakout sessions on Wednesday afternoon focused on three main topics:
(1) GnRH neurons
(2) Polycycstic ovarian syndrome and insulin sensitivity
(3) Diffusive messengers
These sessions mainly consisted of group discussion without a specified moderator. Given that the two plenary speakers on Wednesday talked about GnRH, that session also included some extended question and answer time for Sue Moenter and Yue-Xian Li.

THURSDAY, AUGUST 12

Differential Regulation of FSHβ Transcription by Changes in GnRH Pulse Frequency
Ursula Kaiser (Brigham and Women's Hospital)

Dr. Kaiser began the Thursday talks with a discussion of FSHβ regulation via GnRH pulse frequency. Pulsatility of GnRH is required to stimulate the release of gonadotropin to stimulate luteinizing hormone (LH) and follicle stimulating hormone (FSH). Indeed, depending on pulse frequency, less GnRH can actually give more stimulation. Throughout one's lifespan there are many different relationships between FSH and LH. Dr. Kaiser discussed an example of dysregulation in this system, polycystic ovary syndrome (PCOS). In PCOS, there is an abnormality in the GnRH pulse generator, so that instead of adjusting the pulse frequency over the cource of the cycle, it remains fast. She explained that if we could control pulsatile GnRH patterns, we could treat PCOS, as well as a number of other endocrine disorders (such as hypothalamic amenorrhea, and some types of infertility). With this in mind, she explored the question: how does the cell translate the pulse frequency of GnRH into a decision to make more FSH/LH? FSH and LH share an alpha subunit, but are distinguished by two different beta subunits, FSHβ and LHβ. Each of the three possible subunits has an optimal pulse time to stimulate secretion, so that the balance of FSH/LH can be controlled by pulse frequency. Her group pieced together a signaling pathway yielding FSH up-regulation via Creb phosphorylation for slow pulses of GnRH and FSHβ repression via ICER for fast GnRH pulses.

Ion channels and the control of the hypothalamic pituitary-adrenal (HPA) axis: from molecules to models
Mike Shipston (University of Edinburgh)

Dr. Shipston explored the hypothalamic-pituitary-adrenal (HPA) axis in more detail— his main goal was to engage the audience in the stress axis, and show it as an important system with relatively little modeling attention paid to it. He began by introducing various types of stress, and the idea that while mild stress can be good for us, too much can be quite costly, with over 13 million days off sick every year due to stress. Stress pathways converge on the hypothalamus in the brain, and activate a variety of autonomic and neuroendocrine responses. He introduced the HPA axis of regulation in which neurons in the paraventricular nucleus secrete CRH and AVP, which stimulates ACTH secretion by the anterior pituitary, stimulating glucocorticoid and cortisol release by the adrenals, which in turn inhibits secretion by the hypothalamus and anterior pituitary, forming two negative feedback loops. Like many of the hypothalamic-pitutiary axes, the HPA axis has both circadian and ultradian rhythms. Using a model, they've found that the ultradian rhythms, long assumed to be due to ultradian CRH release, may actually be due to hypothalamic-pitutiary interactions. This leads to a prediction that if CRH is too high or too low the rhythmicity of the system will be lost. He explored these issues further using an ion channel approach, to see how the ion channels were interrelated in affecting the HPA axis.

Breakout Sessions

There were three groups in this session. The first topic was a primer on the stress axis, with this group exploring the HPA axis in more detail. The second group discussed frequency sensitivity of pituitary cells, and the third group explored mixed mode oscillations and bursting.

FRIDAY, AUGUST 13

Multi-Scale Mathematical Models of the Supra-chiasmatic Nuclei
Richard Yamada (University of Michigan)

The central theme of Yamada's talk was the functioning of the supra-chiasmatic nucleus (SCN), which is the organ responsible for coordinating time keeping in all cells in mammals, making it a master-clock. The SCN is composed of approximately 10,000 individual cells. Experimental evidence indicates that each cell in the SCN is an individual oscillator; therefore, it is an interesting problem to understand the important intercellular coupling mechanisms (electrical and chemical) that help in synchronizing rhythms within this cellular network. Dr. Yamada presented a multi-scale mathematical description of these coupling mechanisms in the SCN network, and validated his work by direct comparison with experimental results.
In particular, the role of Bmal1 – an essential transcriptional activator within the mammalian circadian clock – was investigated. Experimentally, an unexpected stochastic rhythmicity in the SCN of Bmal1-deficient mice was reported, which appeared as an emergent network property of the SCN. In order to understand this better, Dr. Yamada modified a previous model of the mammalian circadian clock by Forger-Peskin, to include detailed biochemistry to accurately model intercellular coupling, and crucially, incorporated molecular noise. It was found that this was required to reproduce the experimentally observed stochastic rhythms, providing a novel biological example of noise-induced oscillations. He concluded that the emergence of stochastic circadian oscillations from the SCN network in the absence of cell-autonomous circadian oscillatory function highlights a previously unrecognized level of circadian organization.

Discussion on the future of Mathematical Neuroendocrinology

The final afternoon was spent discussing future directions for mathematical neuroendocrinology. The discussion began by addressing when and where to hold the third workshop in the series, and then mentioned some upcoming events of interest to mathematical neuroendocrinology. Next, the group considered suggestions for how to run the meeting next time around, including how to improve the breakout sessions (perhaps some sessions could have more of a planned set of questions or an expert to organize the discussion, whereas others can be more freeform), possible wiki-style options for planning and suggesting topics, and focus topics for next time (behavioral neuroendocrinology, time scales from neurons to gene regulation, how to extract the relevant information from data for models, and model comparison methods). The idea of organizing some sort of mathematical neuroendocrine society was also discussed, perhaps as an independent group, or perhaps as an activity group within a larger organization (e.g. SIAM, SMB, or the American Neuroendocrine Society).

WORKSHOP FOR YOUNG RESEARCHERS IN MATHEMATICAL BIOLOGY

AUGUST 30 - SEPTEMBER 1, 2010

Organizers: MBI Postdocs

Report written by Shu Dai, Suzanne Robertson, and Chuan Xue

OVERALL SUMMARY

The Fall 2010 Workshop for Young Researchers in Mathematical Biology was held August 30-September 1, featuring three full days of exciting plenary talks, short talks, poster sessions, and panel discussions. The six plenary talks and 12 short talks covered a wide range of topics in mathematical biology. The participants, mainly graduate students, postdocs, and tenure-track faculty, were able to ask questions on topics related to applying for jobs and early career development during the two panels. Thirty-two participants along with the MBI Postdoctoral Fellows presented posters. Two poster sessions and receptions were held in order to accommodate this large number of posters. Poster previews preceded both sessions, with each presenter giving a 1-2 minute introduction to his or her work. The poster sessions and receptions that followed encouraged extensive discussion among the participants of the workshop.

MONDAY, AUGUST 30

Plenary Talk I: Mechanisms of length regulation of flagella in Salmonella
James Keener (University of Utah)

Keener presented mathematical models for the regulation of hook and filament length in motile bacteria such as Salmonella. The length of the hook is tightly controlled, whereas the length of filaments is less so. However, if a filament is broken it will regrow, while a broken hook will not regrow. The model for hook length regulation is based on the hypothesis that the hook length is determined by the rate of secretion of the length regulatory molecule FliK and a cleavage reaction with the gatekeeper molecule FlhB. A stochastic model for this interaction is built and analyzed, showing excellent agreement with hook length data. The model for filament length regulation is based on the hypothesis that the growth of filaments is diffusion limited and is measured by negative feedback involving the regulatory protein FlgM. Thus, the model includes diffusion on a one-dimensional domain with a moving boundary, coupled with a negative feedback chemical network. The model shows excellent qualitative agreement with data, although there are some interesting unresolved issues related to the quantitative results.

Short Talk: Persistence of mass-action biochemical reaction networks
Casian Pantea (University of Wisconsin - Madison)

Persistence has an intrinsic importance in the study of animal population dynamics and in the analysis of infections spread. Pantea showed that a large class of two-dimensional biological interaction network models is persistent. This result is robust, in the sense that it holds independently of the choice of parameters in the model. The persistence result may also be used to prove the three-dimensional case of the Global Attractor Conjecture for biochemical reaction networks, a long-standing conjecture originating in the work of Horn, Jackson, and Feinberg.

Plenary Talk II: Algebraic models in systems biology
Reinhard Laubenbacher (Virginia Tech)

Progress in systems biology relies on the use of mathematical and statistical models for system level studies of biological processes. Several different modeling frameworks have been used successfully, including traditional differential equations based models, a variety of stochastic models, agent-based models, and Boolean networks, to name a few common ones. Laubenbacher focused on several types of discrete models, and described a common mathematical approach to their comparison and analysis, which relies on computer algebra. In this plenary talk, specific examples of biological systems were presented that can be modeled and analyzed in this way.

Plenary Talk III: Kinesin-microtubule interactions: transport and spindle formation
Peter Bates (Michigan State University)

Bates studied the pattern formation in families of microtubules under the action of kinesin and the detailed motion of kinesin along a microtubule. In the first set of results, microtubules are represented as stiff, polar rods that are subject to diffusion in position and orientation and also subject to pair-wise interaction, mediated by kinesin molecular motors. The concentration of kinesin is represented by a parameter that feeds into the probability of an interaction occurring when two microtubules collide. With collision rules in place, Monte-Carlo simulations for large numbers of freely moving microtubules are performed, adjusting parameters for concentration of kinesin and polarity of the microtubules. From these studies, a phase diagram is produced, indicating thresholds for phase change to occur. Simulation results are compared to those from in vitro experiments. The second part of the talk involved modeling the fine scale dynamics of a kinesin motor as it walks along a microtubule. The two heads of the kinesin molecule alternately bind and unbind to the microtubule with certain mechanisms providing a directional bias to the Brownian motion expected. The trailing head detaches from the microtubule and it then becomes subject to the biased entropic force due to the zipped state of the leading head and also preferentially attaches in front of the currently attached head at which time ADP is released and a conformational change occurs, strengthening the binding. This motion is modeled using a stochastic differential equation. Simulations were performed with different lengths of neck-linkers and the mean speeds of progression obtained. These were then compared with experimental results.

Short Talk: Asymmetric stable droplets in a fish patterning model
Thomas Woolley (University of Oxford)

Soliton-like structures called "stable droplets" are found to exist within a paradigm reaction diffusion model that can be used to describe the patterning in a number of fish species. It is straightforward to analyze this phenomenon in the case when two non-zero stable steady states are symmetric; however, the asymmetric case is more challenging. Woolley and his colleagues used a recently developed perturbation technique to investigate the weakly asymmetric case.

Short Talk: Evolution of body size in food webs
Rosalyn Rael (University of Michigan)

Body size has been shown to be a significant factor in shaping the structure of food webs, which are network models of the flow of energy in an ecosystem. Recent studies have shown that body size constraints can influence food web dynamics through prey preference and foraging behavior, and can thereby influence the stability of these ecosystem models. Rael uses body size as the species strategy in an evolutionary game theory approach to studying the influence of predation at individual trophic levels on evolutionarily stable strategies (ESS) in food webs. It is shown that when a consumer is introduced, the equilibrium strategy of the basal species evolves toward a value that increases the intrinsic growth rate. It is also shown how size-based prey preference can influence strategy dynamics and population sizes over long time scales.

John Lowengrub (UC Irvine)

Short Talk: Modeling Neural Circuitry for Early Olfactory Processing
William Erik Sherwood (Boston University)

The neuronal networks of the olfactory system transduce and transform complex mixtures of odorant molecules into patterns of the neural activity representing smells. Sherwood explored two important aspects of how this process works, at the cellular and the neural circuit level, in modeling studies that produce experimental testable predictions. Specialized smooth optimization methods are used to study the (local) sensitivity of its functional characteristics (e.g., burst duration, interburst interval) to parameters, and statistical analyses to characterize the (global) influence of different currents.

TUESDAY, AUGUST 31

Plenary Talk IV: Feedback, lineages and cancer
John Lowengrub (University of California, Irvine)

Lowengrub presented a recent multi-component continuum model he developed to simulate the dynamics of cell lineages in solid tumors. The model incorporates cell proliferation and death as functions of the distributions of oxygen and soluble chemical factors. The model was solved in three spatial dimensions using an adaptive mesh method. Computational results show that the incorporated processes play a critical role in tumor progression and the development of morphological instability, such as fingering from axially symmetric shapes.

Discussion Panel I: Applying for Jobs in Academia

The panelists were the six plenary speakers - Orly Alter, Peter Bates, James Keener, Reinhard Laubenbacher, John Lowengrub, and Van Savage. MBI postdoctoral fellows Harsh Jain and Marisa Eisenberg moderated the panel. During the discussion, the workshop participants asked many interesting questions concerning preparation of application material, interviews, individual talks with the hiring committee, establishing personal contacts, and transition of jobs between industry and academia. The panelists shared their experience and advice on these issues and provided an insider's perspective on the evaluation of job candidates.

Plenary Talk V: Discovery of Mechanisms from Mathematical Modeling of DNA Microarray Data: Computational Prediction and Experimental Verification
Orly Alter (University of Utah)

Alter gave several examples that demonstrate how mathematical modeling of DNA microarray data can be used to correctly predict previously unknown mechanisms that govern the activities of DNA and RNA. She explained how she uses tensor computations to predict correlations between DNA replication initiation and RNA expression, and showed that the predictions were confirmed in recent experiments. She also showed that singular value decompositions can explain asymmetries in microRNA data.

Short Talk: Novel clustering methods for the analysis of biological data
Sijia Liu (Iowa State University)

Liu presented a new fuzzy spectral clustering algorithm that combines the strengths of recent approaches based on spectral graph theory, and fuzzy methods clustering methods. She gave examples, such as facial recognition, showing that her methods outperform other methods.

Short Talk: Optimal control on insect pest population
Delphine Picart (Arizona State University)

Extensive use of pesticides leads to the existence of serious environmental damages and the main objective in agricultural research is to reduce the use of these products. She introduced a multi-stage age-structured population dynamics model that can be used to achieve this goal. The talk focused on the optimization problem of finding the best treatment of a vine pest during the pest life cycle under three constraints: action mode, the price, and the efficiency of pesticides.

Short Talk: Understanding how rapid evolution affects predator-prey systems using fast-slow dynamical systems
Michael H. Cortez (Cornell University)

Cortez presented a recent approach that uses theory of slow-fast dynamical systems to study predator-prey system exhibiting rapid evolution. The method reduces the system down to two dimensions, which is theoretically manageable. He also showed graphical techniques to study qualitative dynamics in a given predator-prey system.

WEDNESDAY, SEPTEMBER 1

Plenary Talk VI: Scaling in Vascular Networks: Curvature, Finite-Size Effects, and Applications to Tumor Angiogenesis and Growth
Van Savage (UCLA Medical Center)

This talk focused on large-scale patterns in biology, specifically how metabolic rate of an organism scales with size and shape. Savage's model is based on a hierarchical, branching network, as the vascular system fuels metabolism. The three basic assumptions are that the energy used is minimized, the vascular system extends to reach all areas of the body, and capillaries, the smallest unit of the vascular system, are invariant in size across all organisms. He discussed some modifications and extensions to this base model, such as finite size corrections, more realistic hydrodynamics, and alternative geometries. At each stage he compared the model predictions to empirical data. For the second half of his talk, he modified these network models to describe the vascular structure and angiogenesis of tumors in order to gain insight into the different stages of tumor growth.

Short Talk: Leg based control of mosquito flight
Sarah Iams (Cornell University)

Iams presented her research in the role of leg motion in the flight of mosquitoes. The body plan of mosquitoes differs from that of other well-studied diptera, such as the fruit fly. The body of the mosquito is more slender, with a wider wingspan and a graceful flight. She used high-speed video and tracking techniques to investigate the importance of the motion of the mosquito's long slender legs in flight. She found that the angular momentum of the legs provides a counter-torque to body roll, and leg motion can modulate excess wing forces. Without their long legs, mosquitoes would have much less finely controlled flight ability.

Short Talk: Modeling and computation of fluid structure interactions near the bell of upside-down jellyfish
Christina Hamlet (The University of North Carolina at Chapel Hill)

Hamlet presented her work on the fluid flow involved in the feeding of the jellyfish Cassiopea. Since this jellyfish is mostly sessile, it provides a unique opportunity to study feeding decoupled from swimming. When the jellyfish feeds, the bottom of the bell slightly suctions to the substrate and it pulses. Structures called oral arms protrude over the bell, changing the flow of water. Christina uses the immersed boundary method to simulate the feeding of the jellyfish and identify key aspects of fluid flow. She looks at the role of the arms on the formation of vortices and the amount of fluid (and thus food) pulled into the jellyfish for a range of Reynolds numbers. She compares her model simulations to data from PIV images from live experiments.

Short Talk: Bistability in Small Networks - Easy to Gain, Hard to Lose
Dan Siegal-Gaskins (MBI)

Specifically, Dan is interested in identifying whether a network has the capacity for multiple stable states from its network topology alone, and how changes in the structure of a network can affect this capacity. To investigate these questions, Dan implemented results of Marty Feinberg from chemical reaction network theory. These theorems allow one to make statements about the number of steady states of a network based on the deficiency of the network (a function of the rank, number of complexes and linkage classes). Using Feinberg's Chemical Reaction Network Toolbox, Dan has classified each of the over 40,000 networks possible when considering the simple biochemistry of two genes as monostable, having the capacity for bistability, or unknown. Dan presented a result ensuring that if you add one reaction to a bi-stable network, without changing the stoichiometric subspace, the resulting network remains bi-stable. This has enabled Dan to classify an additional 46% of networks as bi-stable. Furthermore, in only one instance out of 40,000 did adding a reaction cause a network to change from bi-stable to mono-stable.

Short Talk: Modeling Angiogenesis and Vascular Tumor Growth in 3D
Holger Perfahl (University of Stuttgart)

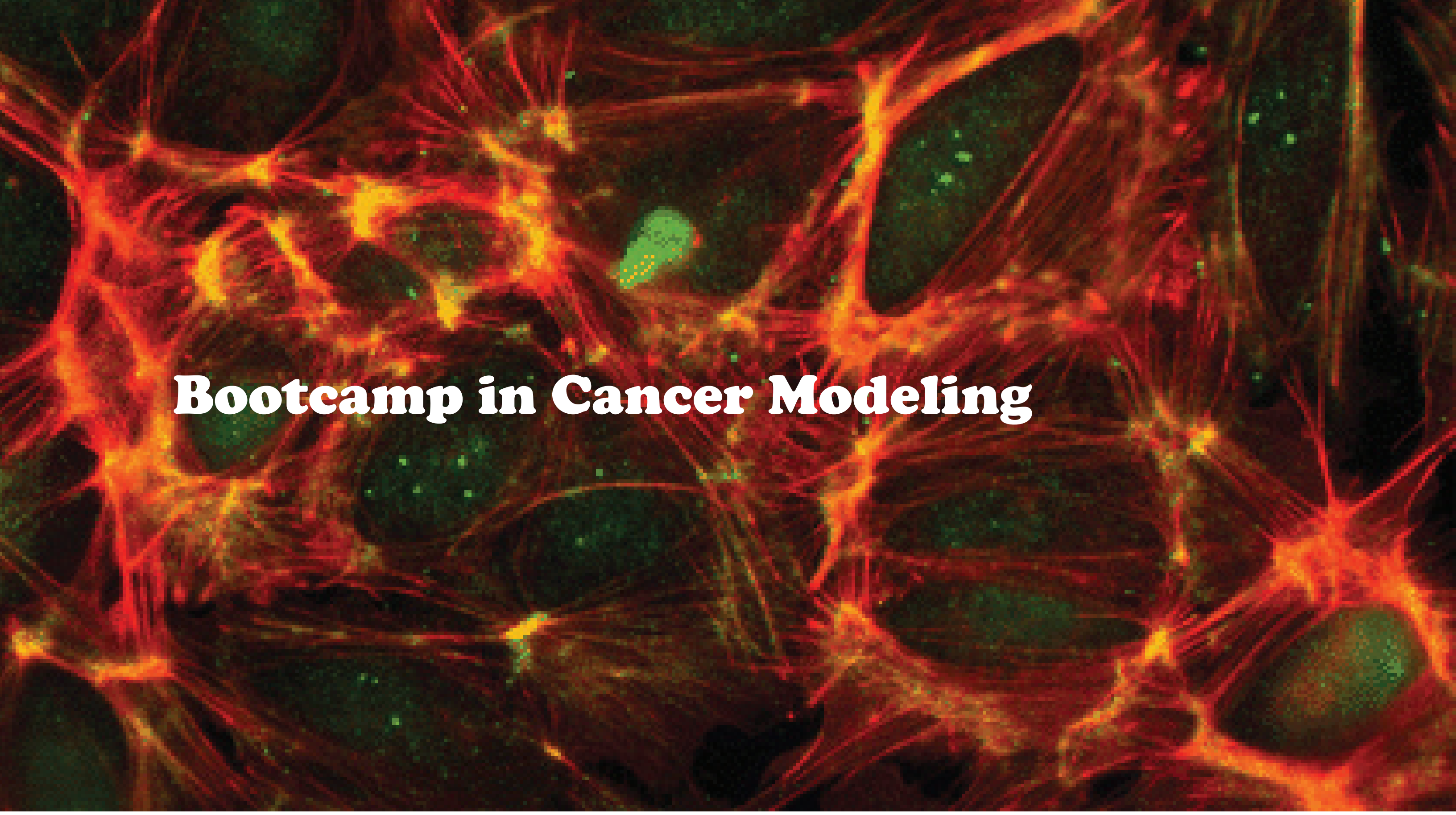
Perfahl developed a multi-part, multi-scale model of tumor growth. He discussed how to connect multiple layers and model the interaction between them, focusing on the differences in vascular structure between tumors and normal tissue. At the sub-cellular level he models the cell-cycle of p53 and VEGF. At the cellular level he models the growth and movement of cells as well as the interaction between normal and tumor cells. At the tissue scale he models diffusion of nutrients and VEGF. Also included is blood flow, angiogenesis and vascular adaptation. Perfahl presented numerical simulations of his model along with hybrid simulations based on the initial real vasculature structure of a rat brain.

Short Talk: Model Reduction in Stochastic Simulation of the Enzyme-Substrate Reaction Set
Kevin Sanft (University of California, Santa Barbara)

Sanft presented his research on a stochastic simulation algorithm (SSA), also referred to as the Gillespie Algorithm. The SSA gives exact trajectories of the chemical master equation that describes the evolution of flux in probability between adjacent states for populations of chemical species; running many realizations gives an approximation to the distribution. Kevin next presented the slow-scale stochastic simulation algorithm (ssSSA), which takes advantage of model reduction, simplifying a set of reactions by removing and/or modifying selected reactions and species, in order to improve the performance and speed of the SSA.

Disscussion Panel II: Career Development in Mathematical Biology

The panelists were plenary speakers James Keener, Orly Alter, Van Savage and Reinhard Laubenbacher, along with The Ohio State University Department of Mathematics faculty members Ching-Shan Chou, Chiu-Yen Kao, and Janet Best. This panel focused on topics relevant to early career development, such as starting collaborations, applying for grants, time management, establishing a balance between work and personal life, and when to take on students. Both panel discussions received excellent feedback from the participants.



Bootcamp in Cancer Modeling

SEPTEMBER 7-10, 2010

Organizers: Helen Byrne (Nottingham University), Mark Chaplain (University of Dundee), Reinhard Laubenbacher (Virginia Tech), Katarzyna Rejniak (Moffitt Cancer Center and Research Institute)

Report written by Harsh Jain, Julia Chifman, and Marisa Eisenberg

OVERALL SUMMARY

The MBI Bootcamp on Cancer Modeling aimed to provide a tutorial and overview of the current state-of-the-art in cancer modeling for young researchers in the biomedical and biological sciences (as well as young mathematical researchers). The bootcamp covered three major themes: radiotherapy, signaling pathways, and tumor growth, each of which was the focus of a morning and afternoon session. For each theme, the first two sessions provided a biological and modeling background and tutorials. These were followed by laboratory sessions at which participants had the opportunity to develop their hands-on skills in model building and/or applications. Each theme ended with a state-of-the art lecture during which the speaker explored current challenges and future research directions. The workshop helped to foster new collaborations between experimentalists and theoretical biologists, and to promote the exchange of mathematical and biological techniques.

TUESDAY, SEPTEMBER 7
INTRODUCTION TO RADIOTHERAPY

Radiotherapy biology: A Primer to Radiobiology in Radiation Therapy

Tyson McDonald (Tufts University)

Dr. McDonald's presentation concentrated on radiation therapy and related radiobiological concerns which include understanding why only half of the patients that receive radiation therapy are cured.

The dogma surrounding radiation therapy is that the normal, healthy tissue rather than the tumor limits radiation therapy. The goal is for enough healthy tissue to survive the therapy and to deliver doses more efficiently better to control the tumor. Current modern treatments include brachytherapy and molecular and chemical targeting.

The speaker emphasized that the physical dose is not necessarily the same as the biological dose. More precisely, the absorbed dose is not uniformly distributed. Further, the biological effect varies with the nature and energy of the ionizing radiation and is dependent on factors that include dose rate, total dose, radiation quality, and tissue type. The definition of ionizing radiation is that the kinetic energy of the radiation has sufficient kinetic energy to remove at least one electron from the atom or molecule. Ionizing radiation is an exogenous stress that has powerful effects on cell death and multiple signaling pathways.

Radiotherapy modeling: The Mathematics of Radiobiology

Philip Hahnfelt (Tufts University)

Dr. Hahnfelt concentrated on two aspects of radiobiology: (1) the quantitative principles of cancer radiotherapy, and (2) the principles of cancer risk estimation. Two types of radiation were discussed. First, we have the type of radiation, such as protons or electrons that can move at a range of velocities.

Second, we have electromagnetic radiation that is confined to move at the speed of light. For the purposes of radiobiology, all the relevant radiations may be thought of as consisting of particles. High doses of ionizing radiation may cause DNA damage in the form of a single or double strand breaks, which may be followed by faulty rejoining. But it is also a fact that radiation in smaller doses can lead to mutations. To take research to the next level, incorporation of important biological effects must be included. A comprehensive, biologically-based model of radiogenic cancer risk should ideally involve all levels of biological organization, from damaged DNA to clinical manifestations of cancer. Such a model would certainly be superior to the phenomenological alternatives currently employed, because it would rely on mechanistic rules to draw upon a broad range of data while also explaining (incorporating?) many of the processes involved in the progression from radiation exposure to developing cancer.

WEDNESDAY, SEPTEMBER 8
RADIOTHERAPY, INTRODUCTION TO SIGNALING PATHWAYS

The radiotherapy computer lab consisted of five tasks: (1) implementing a linear-quadratic model in Microsoft Excel, (2) and (3) counting clones in a clonogenic assay without and after radiation exposure, (4) and (5) performing linear regression on the data and simulation.

Radiotherapy Colloquium: Symbiosis of tumor growth dynamics and radiotherapy modeling
Heiko Enderling (Tufts University)

Dr. Enderling surveyed recent developments in the field of radiotherapy modeling: the linear-quadratic model of radiotherapy, continuous models formulated as differential equations, and discrete models that distinguish individual cells (agents) that reside on a discrete lattice. Although chemotherapy has been simulated, much less attention has focused on formulating and analyzing dynamic models of conventional tumor radiotherapy. Although radiation is widely used, most treatment schedules are based on empirical knowledge and less on the predictions of sophisticated mathematical models of tumor growth and treatment response.

Dr. Enderling also discussed the cancer stem cell hypothesis which postulates the existence of a small subset of cancer cells, the cancer stem cells that constitute a reservoir of self-sustaining cells with the exclusive ability to self-renew. He emphasized that cancer stem cells have two characteristic features that other cancer cells do not: (1) ability to evade apoptosis and (2) a limitless replicative potential. He presented several simulation results demonstrating the impact of the cancer stem cell hypothesis and discussed how experimental and clinical data can be used to estimate stem cell fractions within primary tumors.

Signaling pathways biology: Using Somatic Genomic Variation to Reconstruct Somatic Cell Evolution
Darryl Shibata (University of Southern California)

Dr. Shibata gave a talk on the evolution of human cancer. One of the problems associated with studying cancer evolution in humans is that serial observations without treatment are unethical and impractical. As a result there is usually only one observation of a patient. Dr. Shibata overcomes this problem by employing a molecular phylogeny approach that involves coalescence theory. The main idea is that genomes are near-perfect copies of copies: the greater the time/number

Vito Quaranta (Vanderbilt-Ingram Cancer Center)

of copies since the common ancestor, the higher the pairwise distance between their genomes. By analyzing methylation data, he is able to predict when coalescence occurred. Shibata has used this approach to study highly proliferative human colon crypts, where each crypt contains multiple stem cells. He used crypts from patients with known age, so that the time of the last common ancestor for the crypt was well established, and compared the genomes of cells from the same crypt with those from different crypts. In this way, he was able to study the stem cell lineages of individual colon crypts and to determine whether they were monoclonal or not and how frequently the stem cells divided). Dr. Shibata then applied this technique to cancer, comparing the evolutionary histories of cells from opposite edges of a tumor to find the time to their common ancestor.

Signaling pathways modeling: Modeling Cancer Signaling Pathways and Networks

Baltz Aguda (National Cancer Institute, NIH)

Dr. Aguda described how to build models of cancer signaling pathways using databases, how to analyze signaling pathway models, and how to reduce them to more tractable sub-models. He began by explaining how oncogenes and tumor suppressor genes (TSGs) regulate processes such as the cell cycle, apoptosis, angiogenesis, growth factor signaling pathways, metastasis, and senescence. He also introduced several databases for pathway ontology, pathways, functional modules, and repositories of math models (e.g. biopax.org, pathguide.org, Biocarta, the Biomodels database, and cellML database). Aguda then used a modular approach to develop a model that accounts for the major pathways known to control the cell cycle and apoptosis. He used the resulting model to explain seemingly contradictory experimental data. In particular, he showed that Mir17-92 could act as both an oncogene and a TSG, depending on the environmental conditions.

THURSDAY, SEPTEMBER 9
SIGNALING PATHWAYS, INTRODUCTION TO TUMOR GROWTH

Computer Lab Session of Signaling Pathways

Participants were given two signaling pathways models—one on BCL2 regulation in apoptosis and the other on VEGF receptor binding. Participants simulated each model and investigated bifurcations, tested alternative hypotheses for receptor-binding mechanisms, and the effects of stochasticity and time-delays on the system.

Signaling pathways colloquium: Dynamic Motifs in Cell Biological Systems

Helen Byrne (Nottingham University)

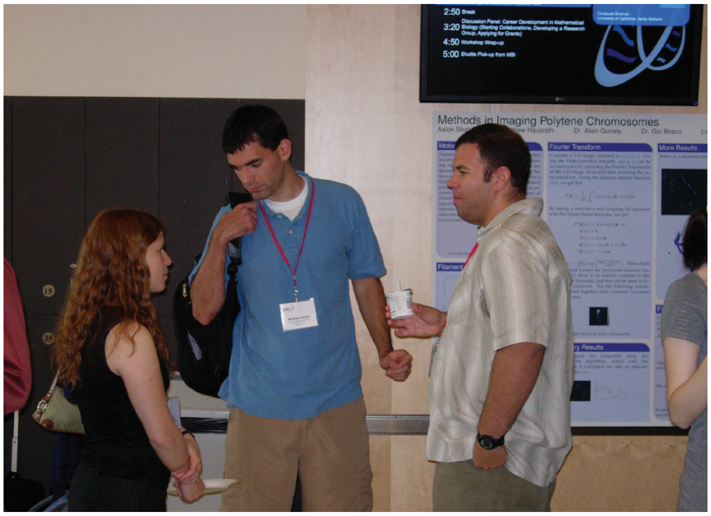
Dr. Byrne gave the final talk in the signaling pathways theme. She began with the apoptosis and VEGF signaling pathways, which had been introduced to in the lab session, noting that it would be natural to combine the models to see how VEGF signaling links to apoptosis and cell death. She pointed out that signaling pathways do not live in isolation—they are coupled together and influenced by external stimuli at multiple scales. This leads to questions when modeling signaling pathways such as: What level of detail is needed? How to approach model simplification? How to incorporate crosstalk between cells and interactions with the microenvironment? How to handle coupling across scales? There are also broader questions that any modeler faces, such as: What question do we want to address the model with and what data is available?

With these issues in mind, Professor Byrne discussed several projects which involved developing mathematical models of the Wnt signaling pathway and early colorectal cancer (CRC). She began by presenting simple models for normal crypt physiology, in which proliferating stem cells at the bottom of the crypt divide and their progeny differentiate and age as they move up towards the top of the crypt where they are eventually sloughed off from the surface. Mutations in the Wnt pathway are common in CRC, and APC is mutated in a large majority of CRCs (one of the earliest elements in the pathway), leading to hyperproliferation and abnormal crypt morphology. Her group has developed a model for Wnt signaling, which initially consisted of 15 ordinary differential equations (ODEs), but could be reduced to seven ODEs and incorporated into multicellular simulations. Their multiscale model has been extended in several ways, to include cell cycle effects, cell adhesion, and migration.

Using these extensions, Dr. Byrne was able to explore several hypotheses and validate the model against data from knockout experiments. She introduced two hypotheses regarding crypt cell behavior: There is direct competition for beta-catenin, one of the components of the Wnt signaling pathway, between movement to the nucleus and movement to the cell membrane, and Wnt regulates this competition. She showed that depending on the parameters, we could see a variety of different behaviors, so that depending on what you measure you may or may not be able to determine how beta-catenin levels are regulated within the intestinal crypt. Her group has also investigated whether stem cells within a crypt are monoclonal or polyclonal. They labeled all cells in a simulation with a different color, and then tracked their progeny over time. They identified conditions that result in monoclonal crypts and also used their model to predict the characteristics that a mutant cell would need in order to establish itself (and/or its progeny) within a crypt.

Tumor growth biology: Systems Biology of the Cancer Cell
Vito Quaranta (Vanderbilt University Medical Center)

Dr. Quaranta reviewed the current state of experimental cancer research and explained how it is merging with quantitative modeling. He focused on the problem of expressing cancer cell biology in the language of Mathematics. This, he argued, was essential in order to increase understanding of tumor growth, particularly the complex ways in which genes and signaling networks interact within cells, to influence their behavior and tissue level dynamics. He noted that over the last decade, the capacity to produce large amounts of data in biology has far outstripped the ability to assimilate and understand it. He concluded by citing an example of the kind of collaboration that can take place between biologists and modelers: his lab, image recognition software has been modified successfully to perform automated measurements of intermitotic times in AT1 cell cultures, grown in the presence of a mitosis inhibitor. The software allows tracking of individual cells, so that daughter cell lineages can also be followed, if required.



Tumor growth modeling: It's not just genes: how interactions drive cancer progression
Sandy Anderson (H Lee Moffitt Cancer Center and Research Institute)

Dr. Anderson presented an overview of the various modeling techniques that his group has developed in order to understand tumor biology. These include from classical reaction diffusion-type of equations to hybrid cellular automata models, immersed boundary methods, and evolutionary game theory. He then presented several examples of models developed in his lab. Specifically, a hybrid framework was used to grow heterogeneous tumors in silico, containing potentially many distinct phenotypes, defined in terms of variations between traits such as cell-cell adhesion, migration speed and proliferation rate. The effect of the tumor microenvironment in selecting for a particular phenotype(s) was evaluated. This in fact led to a novel hypothesis – that invasion is an emergent property of the collective behavior of the cell population under selective pressure from the tumor microenvironment. Dr. Anderson next presented an application of the immersed boundary method to model the development of mammary acini. The model could predict normal and aberrant morphologies under a variety of assumptions on cellular morphology. Recently, his experimental collaborators have devised an experimental assay of a human mammary cell line that displays a number of the morphologies predicted by the model, thus allowing for a means of linking the morphological and molecular scales via computational modeling. He concluded his talk with an example of a feed forward neural network applied to a model of clonal evolution in cancer, the aim of the model being to investigate the emergence of the glycolytic phenotype. Modeling results showed that evolution selects for the glycolytic phenotype, rather than genotype.

FRIDAY, SEPTEMBER 10
TUMOR GROWTH

Computer Lab Session on Tumor Growth
Participants were asked to work on an agent based model of tumor growth on a 2D and 3D lattice, and investigated questions such as the impact of individual cell doubling times on whole populations, or tumor cell phenotype on tumor size, concluding with microenvironmental impact on tumor evolution.

Tumor Growth Colloquium: Multi-Scale Model of Tumor Development: From Molecule to Tissue
Yi Jiang (Los Alamos National Laboratory)

Dr. Jiang presented an approach to modeling solid tumor growth using the Granier-Glazier model (Potts model), in which the behavior of individual cells is determined by an energy minimization principle. This model incorporates cell-cell interactions through a common surface and can account for intracellular signaling pathways (e.g. via a Boolean approach). Dr. Jiang demonstrated the power of the Potts framework by presenting a model of avascular tumor growth and describing how predictions generated by the model about when necrosis is initiated have subsequently been validated experimentally. She argued that this type of modeling is ideal for distinguishing cell level phenotypes and cell-cell interactions. However, it is weighted down by expensive computation, and is not ideally suited to the incorporation of mechanical effects. She also presented a model of tumor angiogenesis that generated spontaneous branching and demonstrated how the structure of the emerging vascular network was influenced by the VEGF isoforms present in the tissue. However, the time scale of vessel growth did not compare well with experimental observations until it was refined to allow for the recruitment of cells from the base of the emerging capillaries to the advancing tip. In the future, the model could be used to investigate the anti-angiogenic potential of drugs like Avastin that target VEGF.

Blackwell-Tapia Conference

NOVEMBER 5-6, 2010

Organizers: James Curry, Martin Golubitsky, Juan Meza, and Cheri Shakuban

Report written by Julia Chiffman and Harsh Jain

OVERALL SUMMARY

This workshop was the sixth in a series of biannual conferences honoring David Blackwell and Richard Tapia, two seminal figures who inspired a generation of African-American, Native American and Latino/Latina students to pursue careers in mathematics. This one and a half day conference:

- Recognized and showcased mathematical excellence by minority researchers;
- Recognized and disseminated successful efforts to address under-representation;
- Informed students and mathematicians about career opportunities in mathematics, especially outside academia;
- Provided networking opportunities for mathematical researchers at all points in the higher education/career trajectory.

FRIDAY, NOVEMBER 5

Simulation of flagellar motions using regularization methods
Ricardo Cortez (Tulane University)

Cortez focused on modeling using the Stokes equations for fluid motion with external forcing. The motivations behind such modeling are: micro-organism swimming, collective motion of bacteria, dynamics of cells, and flows in arteries or channels. Many of these situations require an understanding of fluid motion near a plane wall.

The method developed was a numerical method for computing Stokes flows in the presence of immersed boundaries and obstacles. The method is based on the smoothing of the forces, leading to regularized Stokeslets. The resulting expressions provide the pressure and velocity field as functions of the forcing. The velocity expression can also be inverted to find the forces that impose a given velocity boundary condition.

The results showed features such as an attraction towards the surface and rotations that generate a drag force that allows the flagellum to roll along the surface.

Galloping Gertie Revisited: Demystifying the Collapse of the Tacoma Narrows Bridge
Talitha Washington (University of Evansville)

The Tacoma Narrows Bridge has been of interest to many engineering students that Talitha Washington is teaching. The Tacoma Narrows Bridge opened on July 1st, 1940 and at the time it was the third longest bridge in the world. Unfortunately, winds caused it to oscillate and the bridge earned the name "Galloping Gertie." The bridge collapsed into the Pugent Sound on November 7th, 1940 when wind speed reached only 40 miles per hour.

People asked the question whether it was resonance? The engineers hypothesized that it was resonance. But if we are thinking that it is resonance then it means that wind was blowing at a frequency that matched the bridge. Thus, this scenario is highly unlikely. Vortex shedding was also examined but it failed to explain the bridge's violent twisting.

The rest of the talk focused on the question as to what was the real reason for the collapse of the Tacoma Narrows Bridge. In 1999, Dr. P. Joseph McKenna presented a model that described the bridge's motion and reasons for its collapse. Joseph McKenna states that the real reason for collapse is that a small periodic torsional force combines with a large vertical transient push to produce a rapid transition to a large torsional oscillation as the vertical oscillation is damped away. He concluded that the Tacoma Narrows Bridge collapsed of its nonlinear springs.

Yes, Even You Can Bend It Like Beckham
Edray Goins (Purdue University)

This talk was dedicated to two mathematicians that our math community lost in 2010: David Harold Blackwell and Angela Elyse Grant. Angela Grant was planning to teach a seminar course that focused on different aspects of mathematics and sports. Edray Goins used that as an inspiration for his talk.
The talk was based on the movie "Bend it like Beckham" and the phrase "No one can cross a ball or bend it like Beckham" in a reference to the international soccer player David Beckham and his ability to cause the ball to swerve. The speaker also focused on Tournoi de France and the free kick that was done by Roberto Carlos. The rest of the talk then concentrated on the following question: Is it possible to curve a ball like that again, and how is it possible?
The explanation was based on the paper "The spinning ball spiral" by french researchers Guillaume Dupeux, Anne Le Goff, David Quere, and Christophe Clanet that appeared in the New Journal of Physics. In the paper they provided both experimental and mathematical analyses of a spinning ball in a fluid to show that it must follow a spiral.

Optimization Techniques for Scheduling Adjuvant Endocrine Therapy for Early Stage Breast Cancer
Illya Hicks (Rice University)

Dr. Hicks presented a mixed integer nonlinear programming model of endocrine therapy in breast cancer. Adjuvant endocrine therapy is given to patients after primary surgery, to treat systemic disease. It can be administered in two possible ways – Tamoxifen, which slows down the growth of cancer cells by blocking estrogen receptors, or aromatase inhibitors (AI) that prevent conversion of androgens to estrogen. However, these have severe side effects. Tamoxifen increases the risk of thromoboembolism, and endometrial or cervical cancer, while AI come with an increased risk of heart attacks and bone loss.

Dr. Hicks' goal was to predict an optimal treatment plan by maximizing the disease-free survival percentage at the end of the treatment subject to constraints dictated by the risk of several side effects. The results of his modeling, validated by comparison with actual clinical trials, indicated that Tamoxifen therapy followed by AI administration for as long as side effects were tolerated, was the optimal strategy. This was true especially of patients who have higher risks of cardiovascular disease or fractures. However, in patients with higher risks of thromboembolic events and endometrial cancer, a monotherapy with AI was recommended. He summarized by underlining the need of conducting clinical trials for schedules with short-term first-step Tamoxifen treatment.

Modeling DNA unlinking
Mariel Vazquez (San Francisco State University)

Vazquez's talk was organized into three parts: (1) motivation and what DNA topology is, (2) application to site-specific recombination, and (3) specific enzymes called XerC and XerD and how they unlink DNA molecules.

DNA topology studies geometrical (supercoiling) and topological (knotting) properties of DNA. Virtually every reaction involving DNA is influenced by the topology/geometry of DNA or has topological effects. Enzymes mediate changes in DNA topology and to analyze the action of such enzymes techniques from knot theory and low-dimensional topology are used. The goal is to understand the topological mechanism of binding and strand-exchange using geometry and topology. Site-specific recombination events can induce topological changes on circular DNA. XerC and XerD are two site-specific recombinases of E. coli, which act cooperatively to resolve chromosomal dimers formed by homologous recombination, thus allowing proper segregation at cell division. The site-specific recombination system XerCD mediates sister chromosome unlinking in TopoIV deficient cells. Mariel Vazquez and collaborators provided a proof that under the model's assumptions there is a unique pathway taking any torus link to the unlink.

Talitha Washington (University of Evansville)

David Blackwell Tribute
James Donaldson & William Massey (Howard University and Princeton University (respectively))

James Donaldson spoke about certain aspects of the life of David Blackwell. Blackwell has influenced many different areas of mathematics and his contributions are immense. He has received honorary Doctorate of Science degrees from twelve institutions: Harvard, Yale, University of Illinois, Howard University, Carnegie-Mellon, University of Southern California, Michigan State, Syracuse, Southern Illinois, University of Warwick, National University of Lesotho, and Amherst College. James Donaldson mainly concentrated on David Blackwell's

activities at Howard University. Blackwell came to Howard University in 1944 and three years after was appointed full professor and later a chair of the Mathematics Department. He was at Howard till 1954. James Donaldson also quoted the following:
"… I'm not interested in doing research and I never have been. I'm interested in understanding, which is quite a different thing. And often to understand something you have to work it out yourself because no one else has done it." - David Blackwell

William Massey focused on David Blackwell as a statistician. More precisely, his talk was based on the article "A conversation with David Blackwell," Statistical Science, 1986, Vol. 1. No.1, pp. 40-53.

Carlos Castillo-Chavez (Arizona State University)

SATURDAY, NOVEMBER 6

Parameter Selection for Inverse Problem Formulation
Ariel Cintron-Arias (East Tennessee State University)

Ariel's presentation investigated the problem of finding multiple solutions for unknown parameters from experimental data with a statistical error structure; in particular, parameter identifiability was addressed by utilizing the sensitivity matrix and uncertainty quantifications in the form of standard errors. An algorithm was proposed that selects parameter combinations that can be estimated using an ordinary least-squares (OLS) inverse problem formulation with a given data set in two stages:

1. The algorithm selects the parameter combinations that correspond to full-rank sensitivity matrices;
2. The algorithm involves uncertainty quantification by using the inverse of the Fisher Information Matrix.

Nominal parameter values are used to construct synthetic data sets, and explore the effects of removing certain parameters from those to be estimated using OLS procedures. Then parameter subset combinations are examined in view of their score and the condition number of corresponding sensitivity matrices.

A New SIS Malaria Model with Vector Demography Showing Natural Occurring Oscillations
Miranda Teboh-Ewungkem (Lafayette College)

Dr. Teboh-Ewungkem presented a new way to model the dynamics of malaria transmission by taking into consideration the demography of the transmitting vector. Her aims were to capture the natural oscillations that are known to exist in the prevalence of malaria, and which other models have only been able to simulate by recourse to external seasonal forcing or delay; to provide a new estimate for the basic reproduction number for malaria; and to propose possible areas of control based on modeling results.

Her model was of SIS type – a variant of the classical SIR model, and was able to capture natural occurring oscillations known to occur in the dynamics of mosquito populations, which subsequently led to oscillations in the dynamics of malaria transmission. These were shown to be the result of instability in the nontrivial disease free and endemic equilibriums resulting in a Hopf bifurcation via a threshold parameter directly linked to the basic reproductive number of the disease and the growth weight of the mosquito population. She concluded that in order to fully understand the dynamics of similar indirectly transmitted diseases such as dengue, yellow fever, and Leishmaniasis, mathematical models need to incorporate the demography of the vectors or arthropods that transmit the agents that cause these diseases.

Climate Change: When Data Fail Us
Juan Restrepo (University of Arizona)

Dr. Restrepo delivered a fascinating lecture on the problem of global warming. In his talk, he argued for the need for mathematics in answering the largest technical challenges posed by the Intergovernmental Panel on Climate Change report of 2007: How confident are we about predictions of future climate scenarios. He began by presenting an overview of extensive data in support of global warming. He argued that in order to understand the earth's climate, it is necessary to focus on the oceans as they occupy 70% of the earth's surface, 90% of the earth's livable space, and hold 86% of the earth's cyclable carbon. Additionally, global ocean temperatures have remained fixed at 3C. To understand this, it is important to retain small scale effects such as wave motion on large scale flows such as waves. His group has developed a Lagrangian time filtering approach to transcend these multi scales. It is also important to incorporate precipitous effect on the ocean surface such as wave breaking. However this leads to huge models with 108 degrees of freedom, leading to computations on matrices that have 1016 elements. His group has also found an efficient way using discrete forward adjoint algorithms to handle computing with such objects.

The main focus of Dr. Restrepo's talk was to try and quantify the sensitivity of weather predictions to changes in the initial conditions, and to find a reduced representation of the dy-

Richard Tapia speaks at the Blackwell-Tapia Award Banquet.

namic variability of weather predictions. This, he showed, was possible using evolutionary models and methods in forward sensitivity analysis. One such way was to compute Liapunov vectors to derive the tangent linear model. A significant challenge was the time required for these computations – typically it could take a month to predict weather patterns for tomorrow. It is possible to overcome this by using the approach of bred vectors. However, this results in an ill-conditioned problem. His group was able to develop a modified approach called the ensemble-bred vector, which reduced the uncertainty inherent in the current standard approach.

Finally, Dr. Restrepo spoke about the prediction problem in climate, made worse due to poor quality data. He argued that it was important to understand the source of the data in order to solve the three time-dependent estimation problems central to climate prediction – the retrodiction problem, where we come up with a best estimate of the state up to today; the nudiction problem, where we come up with a best estimate of what's happening at current time; and finally the forecasting problem. He showed that using Bayes Theorem is an effective way of dealing with these problems. However, care must be taken in solving these non-linear non-Gaussian problems. Dr. Restrepo presented effective methods developed by his group such as the diffusion kernel filtering to solve these.

Nonlinear Partial Differential Equation and Stochastic Control
Ryan Hynd (University of California, Berkeley)

Nonlinear partial differential equations arise in stochastic optimal control via dynamic programming equations. In many cases, solutions of these equations aid in the design of optimal controls. Hynd discussed a class of equations where the associated control processes are singular with respect to the time variable. These equations arise in models for spacecraft control, financial models that incorporate transaction costs, and in models of queuing systems. He presented several examples of singular control including the Merton problem relating to optimal portfolio selection with transaction costs. He also presented a few results on the regularity of solutions of such problems, and of problems of singular ergodic control. He concluded with an open problem relating to smoothness of the open boundary of the solutions of these problems.

A Survey of Signal Processing Questions in Neuroscience
Emery Brown (Harvard Medical School and Massachusetts General Hospital & MIT)

Dr. Brown's talk surveyed general anesthesia-induced loss and recovery of consciousness in humans. General anesthesia is a drug-induced, reversible state comprised of unconsciousness, amnesia (loss of memory), analgesia (loss of pain perception), akinesia (loss of movement), and stability and control of the cardiovascular, respiratory thermoregulatory, and autonomic nervous systems. Still, the mechanism by which an anesthetic drug induces general anesthesia remains a medical mystery. A new research direction in Emery Brown's laboratory is to use a systems neuroscience approach to study how the state of general anesthesia is induced and maintained. To do so, they are using fMRI, EEG, neurophysiological recordings, microdialysis methods and mathematical modeling. Dynamics of loss and recovery of consciousness are:

1. Loss of consciousness: decrease in activity across many brain regions and loss of communication between regions;
2. Unconsciousness: strong narrow band coherent activity across the anterior forebrain mediated by thalamocortical loops at 10-13 Hz and slow wave cortical oscillations 0-2 Hz;
3. Return of consciousness: loss of narrow band coherent activity, return of communication between regions.
4. In conclusion, general anesthesia is not a sleep but rather a reversible coma.

The long-term goal of this research is to establish a neurophysiological definition of anesthesia, safer, site-specific anesthetic drugs, and to develop better neurophysiologically-based methods for measuring depth of anesthesia.

How Can Changes in Protein Isomer Concentration Trigger Protein Aggregation Diseases?
Conner Sandefur (University of Michigan)

Sandefur's talk focused on protein aggregation diseases, also called conformational diseases, caused due to protein misfolds wherein the protein is unable to return to its native conformation. For instance, permanent neo-natal diabetes, caused by a misfolding in their proinsulin, and Huntington's disease are examples of these diseases. In some cases, these proteins interact with bystander proteins eliciting a misfolded phenotype. There is evidence to suggest that bystander protein disappearance occurs through direct or indirect interaction with misfolded proteins, resulting in a transformation into aggregate-prone misfolded protein. Protein aggregation in conformational diseases often displays a threshold phenomenon characterized by a sudden shift between nontoxic and toxic levels of protein aggregates. Working with the hypothesis that there is a limited number of ways for the proteins to interact that can result in the manifestation of this threshold phenomenon, Sandefur proposed a general mechanism of bystander and misfolded protein interaction to investigate how this phenomenon in protein aggregation is triggered in conformational diseases. Using a continuous flow reactor model of the endoplasmic reticulum, in which protein folding typically takes place, he derived necessary conditions to produce threshold phenomena, which occurred due to the appearance of bistability in the system.

Sandefur's results indicated that slight changes in the ratio of misfolded to bystander basal protein concentrations could trigger the threshold phenomena in protein aggregation. He further proposed a general mechanism for the loss of function observed in certain conformational diseases, and identified the conditions necessary to trigger the observed threshold phenomena in protein aggregation. He concluded by underscoring the necessity to understand the conditions necessary for the aggregation threshold phenomena as an important step towards developing therapeutic strategies targeting the modulation of conformational diseases.

SUNDAY, NOVEMBER 7

Young Women and Mathematical Biology: A Personal Perspective
Carlos Castillo-Chavez (Arizona State University)

Dr. Chavez delivered an inspiring talk on the present role of women in the field of mathematical biology. Paying tribute to Lee Segel, who in his words was 'an extraordinary mentor of women and his former students include many leaders in the field of mathematical biology', Dr. Chavez gave a series of examples from his own experiences with women mathematicians at the undergraduate, graduate, as well as postdoctoral levels. In particular, he spoke of the High School Mathematics Science Honors Program (MSHP) that has achieved impressive success rates in attracting minorities and women minorities in particular, to higher education in the sciences, despite an increasing rate of high school dropouts in Arizona. Emphasizing the need to attract more women to the sciences, Dr. Chavez pointed to the decreasing percentage of women math and engineering majors at ASU. He then spoke of the contribution of the Mathematical and Theoretical Biology Institute (MTBI) at ASU that has produced a number of success stories such as Dr. Sara del Valle, a permanent member of LANL, who was an Iowa-Sloan fellow at the MTBI. He concluded with a tribute to Dr. Jackson, also a graduate of the MTBI, and winner of the 2010 Blackwell-Tapia Prize.

The Evolution of Hybrid Models of Tumor Angiogenesis
Trachette Jackson (University of Michigan)

Dr. Jackson was the keynote speaker of the conference, and the recipient of the Blackwell-Tapia 2010 Prize. The focus of her talk was on how mathematical models can help understand tumor-initiated blood vessel formation or angiogenesis, and her contribution to this field. One of the challenges in modeling angiogenesis is that it is a highly multi-scale process occurring at several levels of biological organization. She began by giving an overview of past models in the literature, which tended to be highly simplified descriptions of cell or vessel and chemokine behavior using a continuous partial differential equation framework. A sophisticated modification of this approach formed the next generation of models, wherein the cell equation was discretized, and cells treated as individual agents. However, the speaker argued that the molecular, cellular, and tissue level features of these models do not reflect the current understanding of the biology.

Dr. Jackson was interested in incorporating detailed biological descriptions in models of angiogenesis, with a view to molecular therapeutics that control this process, with particular emphasis on VEGF, a key pro-angiogenic chemokine. In order to do this, she developed a hybrid model of VEGF-induced cell migration based on the theory of reinforced random walks, which incorporated VEFG receptor activation on the cell surface. The model predicted realistic dynamics of cell motion such as a minimum activation threshold of receptors and receptor desensitization. Building a model that simulated endothelial cell elongation, proliferation and maturation during angiogenesis brought the next level of sophistication. Discrete points were used to track each cell in the developing sprout, and cellular-matrix interactions explicitly incorporated. With the aid of a variety of simulations, Dr. Jackson showed how this model provided a nice framework for gaining a more in-depth, mechanistic understanding of angiogenesis.

As the final generation of models, she presented a Cellular Potts model of angiogenesis that was built in order to track changes in cell morphology and shape. This type of model is still hybrid, however, it partitions space into different cell types. Thus, cells can change shape and cell-cell or cell-matrix interactions can be explicitly incorporated. Branching and anastomoses were shown to be emergent properties of the model. Dr. Jackson concluded by emphasizing that there is still the need for a comprehensive model of tumor initiation and progression that incorporates all the details mentioned in her talk. Such a model could then be used to aid in the development of novel cancer therapeutics, leading to faster translation times of drugs from 'the bench to the bedside' at significantly lower costs.

New Developments in Dynamical Systems Arising from the Biosciences

MARCH 22-26, 2011

Organizers: Tasso Kaper (Boston University), Bernd Krauskopf (University of Bristol), Hinke Osinga (University of Bristol), Martin Wechselberger (University of Sydney)

Report written by Shu Dai, Casey Diekman, and Chuan Xue

TUESDAY, MARCH 22

Math to Bio and Bio to Math
John Guckenheimer (Cornell University)

This talk gave an overview of how dynamical systems theory and biology have impacted each other in the past, and also showed promising new mathematical problems arising from biology to be addressed in the future. In particular, the speaker reviewed action potentials, Aplysia and Tritonia bursting, and the Belousov-Zhabotinsky reactor as examples that have multiple time scales or can generate mixed modes oscillations. He also demonstrated how to construct traveling wave solutions in the Hodgkin-Huxley and FitzHugh-Nagumo equations using geometric singular perturbation methods. He ended with a discussion of his vision of research on parameter estimation, model reduction, and smooth computational geometry.

Synchronization phenomena in delay-coupled network motifs
Ingo Fischer (Institute for Cross-Disciplinary Physics and Complex Systems)

Coupled nonlinear oscillators can be found in many problems in physics and biology. The presence of sufficiently large time delays in the coupling can give rise to dynamical instabilities. In this talk, the speaker discussed that in laser experiments and modeling, synchronization of the chaotic dynamics can occur via coupling through a relay element. He also discussed how this theory has been extended to models of neuronal networks.

Identifying Compensatory Perturbations in Biological Networks
Adilson E. Motter (Northwestern University)

Motter showed that in food-web networks and intracellular gene regulatory networks, knocking out some of the nodes might cause the system to operate more efficiently or optimally. This phenomena has posed challenging mathematical questions such as how can one combine theory of dynamical systems and network modeling to identify such perturbations that leads to optimized networks, and how does such optimization happen evolutionarily, if indeed it does?

Cross-currents between Biology and Mathematics on Models of Bursting
Artie Sherman (N.I.H.-N.I.D.D.K.-M.R.B.)

Sherman gave a review on models of bursting. He focused on the mathematical study of square-wave bursters, which were first introduced by the Chay-Keizer model of the dynamics of calcium flux inside pancreatic beta cells. The model was analyzed by using John Rinzel's fast-slow analysis, and by considering the full system. Using this example, the speaker showed us that the development of mathematical theory is useful for modelers, but also that theory which generates a limited menu of mechanisms may steer modelers away from potential efforts to find other bursting mechanisms.

Noise sensitivities in systems with delays and multiple time scales
Rachel Kuske (University of British Columbia)

Kuske gave several examples to explain how noise can change dynamical systems with delays and multiple time scales dramatically. She showed models of postural sway and stick balancing, and transferred ideas from those applications to biological ones, for example balance, blood diseases, and epidemiology. She showed how noise can stabilize transient oscillations, and how phenomena at different time scales interact with each other.

Generation and synchronization of oscillations in synthetic gene networks
Lev S. Tsimring (University of California, San Diego)

Tsimring described their recent work on small synthetic gene networks that exhibit oscillatory behavior. The synthetic network consists of a negative feedback loop with delay, and a positive feedback loop. The delay in the negative feedback loop was shown both theoretically and experimentally to be the main reason for the oscillations, while the positive feedback loop only amplifies the oscillation.

WEDNESDAY, MARCH 23

Waves in random neural media
Stephen Coombes (University of Nottingham)

In normal and abnormal brain activities, propagation of waves is a common phenomenon. In the past, integro-differential neural field models were used to model such waves, and for simplicity, these models assume the brain to be a homogeneous medium. However, the brain is very heterogeneous and has very specific structures. Canonically, homogenization can be very useful to capture the dynamics of the brain when the spatially multi-scale structure is present. The speaker presented novel improvement of this approach by considering the heterogeneous environment as a random process.

Geometric singular perturbation theory beyond the standard form
Peter Szmolyan (Technische Universitat Wien)

The standard geometric singular perturbation theory can be applied to analyze biological models with multiple time scales when there is a clear separation of scales into fast and slow. However, there are cases with no global separation of scales, or with more than two time scales involved, or that depend on several parameters singularly, etc. For these problems, one needs to develop new mathematical techniques. In this talk, the speaker illustrated a systematic approach using geometric methods based on the blow-up method to treat these problems using several examples.

John Guckenheimer (Cornell University)

Understanding intracellular calcium dynamics: modelling and mathematics
Vivien Kirk (University of Auckland)

Calcium regulates a wide range of functions of the cell. Oscillations of cytoplasmic calcium have been thought important in processes such as muscle contraction, cardiac electrophysiology etc. Much effort is devoted to the experiments and modeling of calcium dynamics inside a cell, with the goal to uncovering the regulatory mechanisms. The speaker illustrated how these experiments motivated new development of bifurcation theory and geometric singular perturbation theory, and identified areas that need more theoretical work.

Periodic orbits in problems with state-dependent delays
Jan Sieber (University of Portsmouth)

The fourth talk on Wednesday was given by Jan Sieber from the Department of Mathematics at University of Portsmouth. His topic was "Periodic orbits in problems with state-dependent delays." Delays in feedback loops tend to destabilize dynamical systems, inducing self-sustained oscillations or chaos. Jan started with an example on caricature about position control to show how one can reduce the study of periodic oscillations in systems with delay to low-dimensional smooth algebraic systems of equations. The approach works also when the delay depends on the state, a case in which it is not clear in general if the underlying differential equations are smooth dynamical systems. The reduction may be generalized to some neutral equations, but it does not work for homoclinic and heteroclinic connections.

THURSDAY, MARCH 24

Stability analysis for stochastic delay differential equations
Evelyn Buckwar (Heriot-Watt University)

The first talk of today was given by Evelyn Buckwar from the Department of Mathematics at Heriot-Watt University. Her topic was "Stability analysis for stochastic delay differential equations." Stochastic delay differential equations often arise in biosciences as models involving, e.g., negative feedback terms and intrinsic or extrinsic noise. Evelyn showed some examples of applications ranging from stochastic models of human immune response systems, neural networks and neural fields, to genetic regulatory systems. Evelyn reviewed the established stability theory for stochastic delay differential equations, and also reported on some problems and progress for stochastic dynamical systems theory for stochastic delay differential equations beyond the stability analysis of equilibria.

Numerics for stability analysis of delay systems and population dynamics
Dimitri Breda (Universita degli Studi di Udine)

Dimitri Breda from the Dipartimento di Matematica e Informatica at Universita degli Studi di Udine gave the second talk and his topic was "Numerics for stability analysis of delay systems and population dynamics." Dimitri addressed the question of asymptotic stability for equilibria of delay differential equations numerically. The proposed method, based on the discretization of the infinitesimal generator of the solution operator semigroup via pseudospectral differentiation, allows one to approximate the stability determining eigenvalue with spectral accuracy. Dimitri also illustrated recent advances in the numerical stability analysis of delay systems and showed how equilibria (characteristic roots), periodic orbits (Floquet multipliers) and chaotic motion (Lyapunov exponents) can be handled under the same discretization framework.

Bounded noise: bifurcations of random dynamical systems
Ale Jan Homburg (University of Amsterdam)

The third speaker in the morning was Ale Jan Homburg from KdV Institute for Mathematics at University of Amsterdam. The topic of his talk was "Bounded noise: bifurcations of random dynamical systems." Random dynamical systems with bounded noise can have multiple stationary measures with different support. Under variation of a parameter, such as the amplitude of the noise, bifurcations of these measures may occur. Homburg discussed such bifurcations both in the context of random diffeomorphisms and of random differential equations.

Phase Models for Oscillators with Time Delayed Coupling
Sue Ann Campbell (University of Waterloo)

Sue Ann Campbell from the Department of Applied Mathematics at University of Waterloo gave the fourth talk in the morning and her topic was Phase Models for oscillators with time-delayed coupling. The speaker considered a network of inherently oscillatory neurons with time delayed connections and then reduced the system of delay differential equations to a phase model representation. She showed how the time delay enters into the reduced model. For the case of two neurons, she discussed how the time delay might affect the stability of the periodic solution leading to stability switching between synchronous and antiphase solutions as the delay is increased. Numerical bifurcation analysis of the full system of delay differential equations is used to determine constraints on the coupling strength such that the phase model is valid. The speaker considered both type I and type II oscillators.

FRIDAY, MARCH 25

Noisy oscillators
Bard Ermentrout (University of Pittsburgh)

The first talk today was given by Bard Ermentrout from the Department of Mathematics at University of Pittsburgh and his topic was "Noisy oscillators." Synchronous oscillations occur throughout the central nervous system, which is sometimes observed across multiple recording sites and over distant brain areas. While local circuitry in cortex is ideal for the production of local rhythms, the mechanisms for synchronization across different regions are more complex. Bard analyzed the role of noise in synchronizing and desynchronizing coupled oscillators using a particular class of simple model oscillators by significantly reducing the dimensionality of the problem, and treating each oscillator as a single variable coding its phase. He first studied a pair and then a large network of globally coupled oscillators using population density methods.

Vivien Kirk (University of Auckland)

Dynamic-clamp studies of neuronal synchronization
John A. White (University of Utah)

John White from Biomedical Engineering at University of Utah gave the second talk and his topic was "Dynamic-clamp studies of neuronal synchronization." Coherent neuronal activity is ubiquitous and presumably important in brain function. John reviewed his group's experimental studies of the mechanisms underlying coherent activity using dynamic clamp technology, which allows them to perform virtual-reality-inspired experiments in neurons in vitro. Using these techniques and mathematical tools from dynamical systems theory, they determined which factors give rise to stable neuronal synchronization in the presence of heterogeneity, noise, and conduction delays.

The effect of noise on mixed-mode oscillations
Barbara Gentz (University of Bielefeld)

The third talk was given by Barbara Gentz from the University of Bielefeld. Her topic was "The effect of noise on mixed-mode oscillations." Many neuronal systems and models display so-called mixed-mode oscillations (MMOs) consisting of small-amplitude oscillations alternating with large-amplitude oscillations. Different mechanisms have been identified which may cause this type of behaviour. In this talk, Barbara focused on MMOs in a slow-fast dynamical system with one fast and two slow variables, containing a folded-node singularity. The main question addressed was whether and how noise may change the dynamics. She showed the existence of a critical noise intensity beyond which the small-amplitude oscillations become hidden by noise. Furthermore, she also showed that an early-jump mechanism can drastically change the mixed-mode patterns, even for rather small noise intensities.

Dynamics of Differential Equations with Multiple State Dependent Delays
Tony Humphries (McGill University, Montreal)

Tony Humphries from McGill University gave the fourth talk of today and his topic was "Dynamics of differential equations with multiple state dependent delays." The Mackey-Glass equation is a seemingly simple delay differential equation (DDE) with one fixed delay which can exhibit the full gamut of dynamics, from a trivial stable steady state to fully chaotic dynamics, and has inspired decades of mathematical research into DDEs. However, much of that research has focused on equations with fixed or prescribed delays, whereas many biological delays would be more naturally modelled as state-dependent delays. Before incorporating state-dependent delays in complex biochemical network models, it is desirable to understand the dynamics that result from including state-dependent delays in simpler models. In this talk he considered a problem with multiple state-dependent delays, and showed that it can exhibit a wide range of dynamical behaviour, including stable periodic solutions and bi-stable periodic solutions, to stable tori, together with the associated bifurcation structures.

Arthur Sherman (NIH-NIDDK-LBM)

Gaits, Gait Obstacles and Gait Assays
Daniel E. Koditschek (University of Pennsylvania)

Dan Koditschek's talk covered a wide range of fascinating developments in the domain of dynamically dexterous legged robots, and showed some very cool video clips of such robots in action. His group has been developing gait generators and gait transition mechanisms. The gait complex and its combinatorially punctured variants have characteristic topological signatures that constrain the manner in which the basins of distinct attracting limit cycles achieved by smooth controllers can fit together. Such constraints impact the engineering of dynamical gait controllers for robots and to the extent that animal motion controllers target smooth dynamical systems, they must impact the animals' designs as well. Dan closed by speculating that if biological preflexes (i.e., those animal motion controllers implemented by the tuned musculoskeletal system) must be smooth, then observations of animal gait transitions may help gain greater insight into the boundary between neural and mechanical control.

Dynamics of neuronal networks as models of visual cortex
Lai-Sang Young (New York University)

Lai-Sang Young discussed her work modeling a small patch of layer 2 of the primary visual cortex (V1) as a large network of point neurons. Network architecture was chosen to reflect a few coarse structures of V1. Her aim was to understand macroscopic observations from dynamics on the neuronal level. Using biological data to constrain parameters, she arrived at models that exhibit a number of empirically observed V1 phenomena (including e.g. localized receptive fields and spontaneous pattern formation in background). Lai-Sang's talk focused specifically on the dynamical mechanisms behind a phenomenon called surround suppression.

From spiking cortical cells to decisions and actions: Some neuroscience problems that I don't really understand
Philip Holmes (Princeton University)

Phil Holmes talk was delivered on Friday night, at the banquet honoring John Guckenheimer's 65th birthday. Phil told the story of how “the book” (Guckenheimer and Holmes, 1983) came to be, and some other personal anecdotes. He also discussed his recent research reducing a spiking model with neuromodulation to a leaky accumulator model. Leaky competing accumulators and drift-diffusion models can reproduce reaction time distributions and other behavioral measures of decision making remarkably well, but they often fail to capture firing rate dynamics in relevant brain areas through the entire course of a trial. The lateral interparietal area (LIP), in particular, exhibits ramping firing rates that track evidence accumulation, but EEG and fMRI studies suggest that a distributed network of cortical areas is involved, and experiments on scanning and attending to multiple stimuli show that LIP reflects processes other than simple integration. Holmes talk touched on several unsolved problems, such as “How can mathematical models engage these data without degenerating into massive, incomprehensible simulations?”

SATURDAY, MARCH 26

Type III Excitability
John Rinzel (New York University)

John Rinzel’s talk began by reviewing Hodgkin’s classification system of nerve excitability and the corresponding mathematical framework. In Type I and Type II neurons, steady input leads to the onset of repetitive firing, while in Type III neurons it does not. Some examples of Type III cells are the squid giant axon (even though the original Hodgkin-Huxley model is Type II), thalamo-cortical relay neurons, and in the auditory brain stem. In the auditory system, the phasic firing of Type III neurons can phase-lock with very high precision. This property might be useful for coincidence detection, the coding of interaural time differences, and ultimately sound localization. Rinzel discussed ongoing work involving a reduced model of medial superior olive (MSO) neurons and dynamic clamp to understand how interaural time differences can be detected at very high resolution by basing the computation on slope detection rather than the amplitude and duration of the signal.

Phil Holmes speaks at the Banquet Dinner.

Computing 2D invariant manifolds: Can you do this?
Hinke Osinga (University of Bristol)

Hinke Osinga’s talk considered the Lorenz system, a classical example of a seemingly simple dynamical system that exhibits chaotic dynamics. In fact, there are numerous studies to characterize the complicated dynamics on the famous butterfly attractor. Her talk addressed how the dynamics is organized more globally, where the stable manifold of the origin (also known as the Lorenz manifold) plays an important role. Hinke told a story about how in 1992, John Guckenheimer suggested this manifold as a bench-mark challenge for developing computational methods in dynamical systems. Hinke showed how the numerical continuation of orbit segments can be used to investigate and characterize the transition to chaos in the Lorenz system.

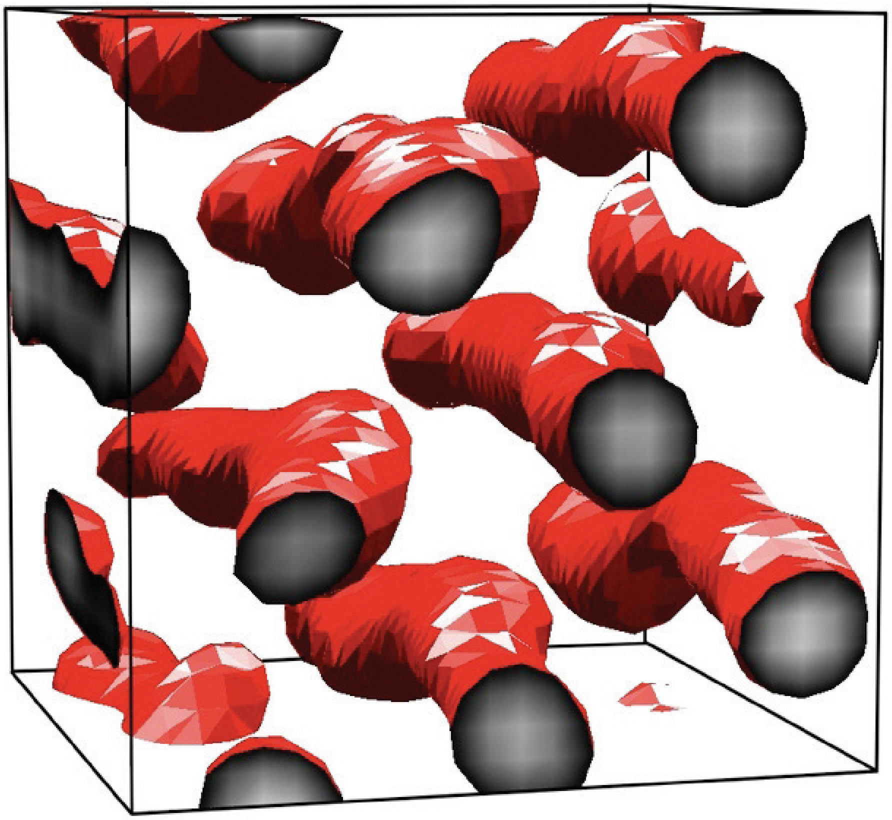
Animal gaits and symmetries of periodic solutions
Marty Golubitsky (MBI)

In the first part of his talk, Marty Golubitsky briefly described previous work on quadruped gaits, where different gaits are distinguished by their spatio-temporal symmetries. By reasoning through the symmetries, they constructed the simplest network model that could support walk, pace and trot as independent gaits. This model made predictions about other gaits, e.g. “jump”, which seemed very reasonable. However, this work assumed that the only way to get periodic solutions on a network with rigid phase-shift synchrony is by having symmetry. In the second part of his talk, Marty discussed this assumption and described how the application of gaits has led to general results about phase-shift synchrony in periodic solutions of coupled systems of differential equations. Marty showed that rigid phase shifts can occur without there being symmetry in the original network, but if and only if there is symmetry in the underlying quotient network. This work was joint with David Romano, Yunjiao Wang, and Ian Stewart.

Modeling Neural Networks for Rhythmic Movements
Ronald Harris-Warrick (Cornell University)

Ron Harris-Warrick’s talk was about central pattern generators (CPGs), which are limited neural networks that drive rhythmic behaviors such as locomotion, respiration and mastication. Ron’s group has been studying the structure, function, and modulation of CPGs, with an emphasis on neuronal and ionic mechanisms that allow flexibility in the output from an anatomically defined network. Both biological and modeling studies show that individual oscillatory neurons can be modulated to generate bursting activity by a variety of independent ionic mechanisms, allowing flexibility in the frequency and output properties of these important neurons. The phasing of neuronal activity in the rhythmic pattern is not determined only by the pattern of synaptic connections; the intrinsic electrophysiological properties of the neurons also play a major role. These points raise issues with regard to the appropriate level of complexity in models of neural networks. Ron discussed these issues based on work done in collaboration with John Guckenheimer on the pyloric network in the crustacean stomatogastric ganglion and the rodent spinal locomotor CPG.

Modeling and Computation of Biomolecular Structure Dynamics



APRIL 25-28, 2011

Organizers: Guowei Wei (Michigan State University), Terrence Conlisk (Ohio State University), Charles Bell (Ohio State University)

Report written by Sam Handelman, Dan Siegal-Gaskins, and Kun Zhao

MONDAY, APRIL 25

Hydrogen-Bond Networks and Membrane Protein Function
Stephen H. White (University of California, Irvine)

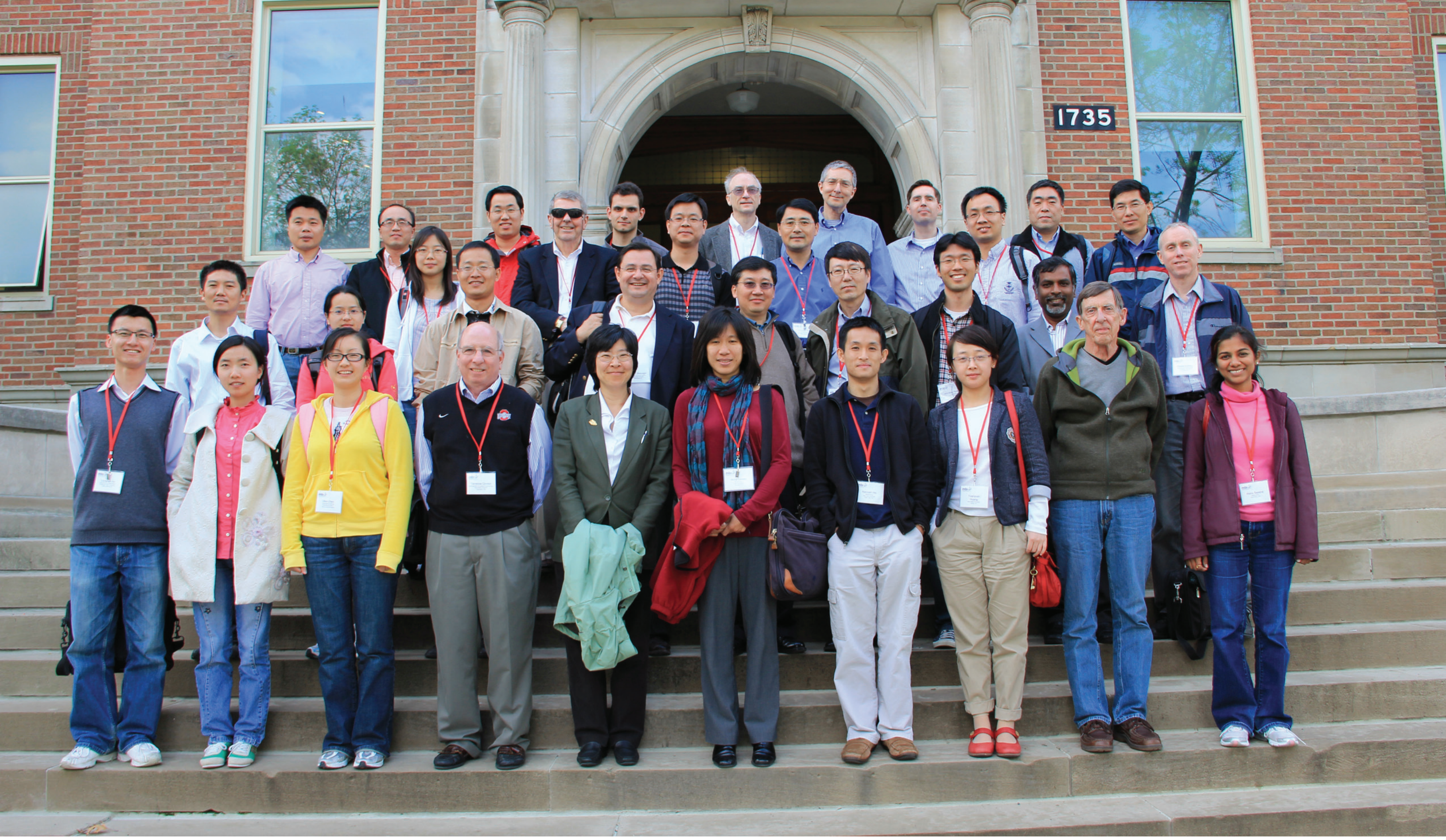
Dr. White discussed the three-dimensional crystallographic structures of membrane proteins, which show static structures obtained from crystalline arrays of detergent-solubilized protein. It was pointed out that although these structures are revealing, two important aspects of membrane proteins are missing: the lipid bilayer environment and protein dynamics. White mentioned that these missing pieces can only be restored using molecular dynamics simulations. He and his collaborators are currently examining several important membrane proteins using this approach. However, the focus of his talk was on the intramembrane protease GlpG and the protein translocase SecYEG. It was shown how dynamic hydrogen-bond networks allow efficient transmission of localized structural perturbations throughout proteins. The results showed the importance of thinking beyond static structural images when considering the regulation of membrane protein function.

Structure Determination of Membrane Proteins in Proteoliposomes
Stanley J. Opella (University of California, San Diego)

Determining the structures of membrane proteins in their native environment of phospholipid bilayers is a major goal of experimental structural biology. Dr. Opella discussed a general method for determining the structures of membrane proteins in proteoliposomes under physiological conditions. The method results from a merger of oriented sample (OS) solid-state NMR and magic angle spinning (MAS) solid-state NMR. It does not require sample orientation, but instead relies on the rotational diffusion of membrane proteins about the normal of liquid crystalline bilayers. This averages the powder patterns of the dipolar coupling and chemical shift powder patterns in a characteristic way, depending upon the orientation of the bond or chemical group with respect to the bilayer normal. The angular constraints are equivalent to those obtained from aligned samples, and can be used as input for de novo structure determination of membrane proteins. Both structural and dynamic data emerged from the analysis, providing insight into the functions of these proteins.

Discrete differential geometry of curves and protein structure
Jack Quine (Florida State University)

Dr. Quine discussed the use of differential geometry techniques in solving an alpha helical structure using NMR. Differential geometry of curves uses the Frenet-Serret moving frame. A curve can be defined by scalar quantities of curvature and torsion and these quantities are defined by differentiating the frame. Similar techniques can be used for discrete



curves formed by sequences of bonded atoms. The frames are related to molecular frames and are useful in finding protein structure from NMR data which gives the orientation of the frames with respect to the magnetic field direction. Curvature and torsion can be related to helical protein secondary structure.

Probing Membrane Protein Structure and Dynamics by NMR and Single Molecule Fluorescence
Lukas K. Tamm (University of Virginia)

Structures of membrane proteins have been challenging to solve by any structural technique. Dr. Tamm discussed recently developed solution NMR spectroscopy as a tool to study the structure and dynamics of membrane proteins, including bacterial outer membrane porins. This class of membrane proteins has proven particularly beneficial for these studies because (i) a larger chemical shift dispersion of residues is observed in ?-sheets than in ?-helices and (ii) much larger numbers of long-range NOEs can be observed in ?-sheet vs. ?-helical membrane proteins. Tamm illustrated progress in this area with the small ion pore OmpA. By using electrophysiological and thermodynamic approaches, he and his collaborators studied the gating of the OmpA ion channel. Attempts to correlate these findings with dynamical properties of the protein were illustrated. It is demonstrated that structural refinements can be obtained by including residual dipolar couplings and paramagnetic relaxation enhancements. The methods have also been extended to solving the solution structure of the 33 kDa pH-gated porin OmpG embedded in a protein/DPC complex estimated to be about 80-90 kDa.

ReplicOpter: A Replicate Optimizer for Flexible Docking
Julie Mitchell (University of Wisconsin-Madison)

Dr. Mitchell presented a computationally efficient method for flexible refinement of docking predictions that reflects observed motions within a protein's structural class. Using structural homologs, she and her collaborators derived deformation models that capture likely motions. The models or "replicates" typically align along a rigid core, with a handful of flexible loops, linkers and tails. It was discovered that a few replicates can generate a much larger number of conformers, by exchanging each flexible region independently of the others. In this way, 10 replicates of a protein having 6 flexible regions can be used to generate a million conformations of a molecule. While this has obvious advantages in terms of sampling, the cost of assessing energies at every conformer is prohibitive, particularly when both molecules are flexible. The approach used by Mitchell and her collaborators addresses this combinatorial explosion, using key assumptions to compress the sampling by many orders of magnitude. ReplicOpter can perform hierarchical clustering from a list of rigid docking predictions and find nearby structures to any promising cluster representatives. These predicted complexes can then be refined and rescored. ReplicOpter's scoring function includes a Lennard-Jones potential softened using the Anderson-Chandler-Weeks decomposition, a desolvation term derived from the Atomic Contact Energy function, Coulombic electrostatics, hydrogen bonding, and terms to model pi-pi and pi-cation interactions. ReplicOpter has performed well on several recent CAPRI systems. The research team is currently benchmarking ReplicOpter on the complete docking benchmark set to fully establish its utility in refining rigid docking predictions and

Julie Mitchell (University of Wisconsin-Madison)

identifying near-native solutions.

Analysis, prediction, and design of viral RNA secondary structures
Christine E. Heitsch (Georgia Institute of Technology)

Dr. Heitsch discussed recent progress made by her research team on the understanding of how biological sequences encode structural and functional information. For RNA viral genomes, the information encoded in the sequence extends well-beyond their protein coding role to the role of intra-sequence base pairing in viral packaging, replication, and gene expression. Heitsch discussed a recent investigation, performed by her research team, of the compatibility of predicted base pairings with the dodecahedral cage known from crystallographic studies, by working with the Pariacoto virus as a model sequence. In order to build a putative secondary structure, different possible configurations using a combinatorial model of RNA folding was first analyzed. Research results on the trade-offs among types of loop structures, the asymptotic degree of branching in typical configurations, and the characteristics of stems in "well-determined" substructures are reported during the presentation. These mathematical results yield insights into the interaction of local and global constraints in RNA secondary structures, and suggest new directions in understanding the folding of RNA viral genomes.

TUESDAY, APRIL 26

Geometric flow for biomolecular solvation
Nathan Baker (Pacific Northwest National Laboratory)

Implicit solvent models are important components of modern biomolecular simulation methodology due to their efficiency and dramatic reduction of dimensionality. However, such models are often constructed in an ad hoc manner with an arbitrary decomposition and specification of the polar and nonpolar components. Dr. Baker reviewed current implicit solvent models and suggested a new free energy functional which combines both polar and nonpolar solvation terms in a common self-consistent framework. Upon variation, this new free energy functional yields the traditional Poisson-Boltzmann equation as well as a new geometric flow equation. Numerical methods for solving these equations are described and comments on future research directions in this area are made.

Image approximations to reaction fields in inhomogeneous media
Wei Cai (UNC, Charlotte)

Dr. Cai reviewed the recent development of image charge approximations to the reaction potential field in Poisson and Poisson Boltzmann solvation models. The following types of inhomogeneous media are discussed: a dielectric sphere embedded in a purely water and an ionic solvent; a layered electrolyte solutions and a model ion-channel model where a finite cylinder is surrounded by layered membrane dielectric/electrolyte solutions. It is demonstrated that the image approximations allow fast multiple algorithms to be used for the electrostatic interactions in molecular dynamics simulations based on hybrid (explicit/implicit) solvation models of biomolecules or ion-channels.

Pseudo-time coupled smooth interface models for biomolecular solvation calculations
Shan Zhao (University of Alabama)

Dr. Zhao presented a recently developed model which extends the standard smeared interface model by considering a generalized nonlinear Poisson-Boltzmann (PB) equation in order to account for the salt effect for the analysis and computation of the equilibrium property of solvation. A new pseudo-time coupling between the surface geometric flows and electrostatic PB potential is introduced. Such a coupling allows for a fast numerical solution of governing nonlinear partial differential equations. Example solvation analysis of both small compounds and proteins are carried out to examine the proposed models and numerical approaches. Numerical results are compared to the experimental measurements and to those obtained by using other theoretical methods in the literature.

In silico modeling of the effects of missense mutations causing mental disorders
Emil Alexov (Clemson University)

Human DNA sequence differs among individuals and the most common variations are known as single nucleotide polymorphisms, or SNPs. Studies have shown that non-synonymous coding SNPs (nsSNPs - SNPs occurring in protein coding regions which lead to amino acid substitutions) can be responsible for many human diseases or cause the natural differences among the individuals by affecting the structure, function, interactions, and other properties of expressed proteins.

Alexov reported recent progress on the investigation of human DNA, especially SNPs. Of particular interest for the research team are rare missense mutations causing mental disorders by affecting the wild type characteristics of a certain protein. The focus of this talk is on three cases: spermine synthase, CLIC2 and SLC8A6 proteins, and missense mutations, which were clinically shown to cause mental disorders. It is demonstrated that in vast majority of the cases the mutations do not directly affect the functional properties of the corresponding protein, but rather indirectly alter its wild type characteristics. Furthermore, the effects caused by disease-causing missense mutations and naturally occurring harmless nsSNPs are compared. It is demonstrated that disease-causing mutations do not necessary destabilize protein stability or protein-protein interactions, but can be stabilizing and still be harmful. Overall, it is pointed out that a detailed computational analysis combined with an analysis of the corresponding biological function is needed to make reasonable prediction of the nature of the missense mutation.

Mathematics in drug design
Ridgway Scott (University of Chicago)

Dr. Scott discussed how mathematics can help in the complex process of drug discovery. He gave an example of modification of a common cancer drug that reduces unwanted side effects. The mathematical model used to do this relates to the hydrophobic effect, something not yet fully understood. The hydrophobic effect modulates the dielectric behavior of water, and this has dramatic effects on how drugs are processed. It is pointed out that future mathematical advances in this area promise to make drug discovery more rational, and thus more rapid and predictable, and less costly.


Ridgeway Scott (University of Chicago)

What can the Poisson-Boltzmann equation teach us about the role of electrostatics in Charged Ligand-Nucleic Acid Association
Marcia Oliveira Fenley (Florida State University)

Prof. Fenley presented a combination of experimental and mathematical/computational approaches to elucidate the role of electrostatics in protein binding. First, Fenley defended implicit solvent models as a computational approach. For computational approaches, computational complexity requires this continuum approximation of the ions surrounding the protein, and these implicit models generally agree well with experimental results. She finished her introduction with useful caveats regarding the proper method to solve the Poisson-Boltzmann equation in different biological contexts. Fenley is specifically interested in DNA/Protein interactions. DNA-binding proteins are particularly promising for this overall approach because of their highly-characteristic surface electrostatics; she reviewed the particular biophysics of several such proteins, along with the biophysics of DNA itself. Referring back to her own introduction, these surface electrostatics, especially of nucleic acids (RNA and DNA), can influence the distribution of ions in the surrounding solvent, complicating the continuum approximation discussed previously. Furthermore, different approximations of the Poisson-Boltzmann equation produce qualitatively different approximations of the solvent characteristics (especially ion concentrations) close to the nucleic acid chain. This is of critical importance, because ion concentrations have a strong effect on the energetics of binding. Finally, she presented a sensitivity analysis on the binding energy to the log of different ion concentrations, comparing different modeling assumptions and nonlinear vs. linear solutions to the Poisson-Boltzmann equation. The salt sensitivity of the binding energy depends on the entire electrostatic surface of the ligands and not just on the residues in the binding interface.

Statistical Measures on Residue-Level Protein Structural Properties
Zhijun Wu (Iowa State University)

Dr. Wu extended the existing statistics on bond angles and distances in proteins (e.g. in Ramachandran plots) to "virtual bond lengths", "virtual bond angles" and "virtual tortion angles" which characterize multiple sequential residues rather than residues individually. In principle, this can be used to guide larger molecular dynamics studies, optimization of crystal structure data, and so forth. First, Dr. Wu showed histograms illustrating the sequential auto-correlation between the tortion angles in adjacent residues from high resolution crystal structures obtained from the PDB, showing both secondary structure effects and signatures from specific series of residues. Second, Wu illustrated how these virtual bond angles can be used to calculate potential energies for different protein structures. He gave an example pair of protein structures where the higher-resolution structure is in much better agreement with his virtual properties. Their software, PRESS, is free to download.

Theoretical and Computational Modeling of Passive and Active Biogels
Qi Wang (University of South Carolina)

Dr. Wang began by endorsing the merits of GPUs as a platform for high performance computing, emphasizing their high power and low cost. Following this, he explained that a biofilm is a structure, mostly water, but containing bacteria held together by extracellular polymeric substances (EPS). Wang gave a summary of the life cycle of bacterial biofilms. These biofilms, especially "flat" biofilms encased by dense EPS, are a major challenge from a therapeutic standpoint, partially because they have limited permeability to small molecule drugs. He uses a network model to represent the biofilm, incorporating nutrients, kinetic and conformational properties, and fluidics. Finally, Wang presented solutions to these models on various scales, with good general agreement with biofilm structures (wrinkles, "mushrooms") which are observed experimentally.

Brad Rovin (Ohio State College of Medicine)

WEDNESDAY, APRIL 27

Ions in Channels: important biology ready for mathematical analysis
Bob Eisenberg (Rush University Medical Center)

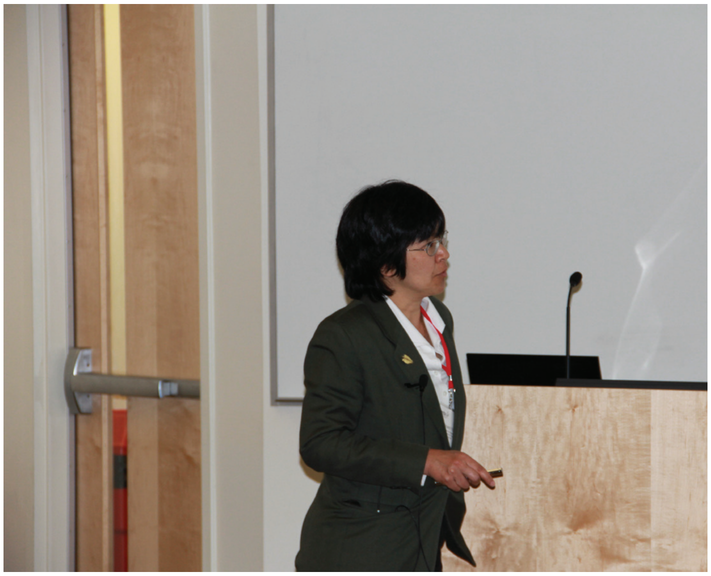
Prof. Eisenberg opened by describing an epiphany: while out camping in the wilderness, he had no access to the fruits of modern industrial civilization, which in turn arise from the application of mathematics. Therefore, this is a good way to explain the utility of mathematics to "ordinary people" (cf. biologists) who do not use mathematics in their everyday lives. He then emphasized the general importance of ions and ion channels to biology and medicine, giving numerous examples. Because of their medical importance, thousands of people study ion channels, including hundreds of people using the "patch clamp" which he co-developed. The particular properties of ion channels – they are a two-state system, and while they are "open" the current is constant regardless of the duration. This has implications for mathematical modeling of the channel properties, in particular it shows that the average structure over short timescales for the "open" channel is constant while the channel is open. This helps to resolve issues that arise in general with atomic simulations, which can be severe both in terms of biological relevance and computational complexity. Next, Eisenberg discussed long-standing issues in existing models of Brownian motion, from a highly quantitative standpoint. Crucially, these models tend to ignore charges, which have a strong qualitative impact on the diffusion of most biological molecules, which are charged, and is crucial in the case of ions. Furthermore, he pointed out that all biological systems are governed by non-equilibrium thermodynamics, since equilibrium biological systems are dead. However, a direct derivation of equations gives PDEs providing the location of individual particles, and, to Eisenberg's surprise, gives the Nernst-Planck equation exactly! However, the electric force probability is conditional on the position of the particle, which is a tremendous issue and is not the same as an actual probability. In an effort to resolve this issue, equations from semiconductors were integrated into the Nernst-Planck framework to produce "Poisson-Nernst-Planck" equations, which are known to be incorrect but provide an initial standpoint to guess experimental results. Because ion channels, like semiconductors, are "devices" (in the technical sense), they are best treated using PDEs with non-uniform boundary conditions; another area where Prof. Eisenberg suggests much more work needs to be done. Inverse problem theory, however, is the relevant branch of mathematics to evaluate the relationship between the "guesses" of these models and the experimental results. The problem, which is fundamentally incompatible with the assumptions behind the ideal gas law, is how ion channels are able to distinguish different ions by their diameter. The solution to inverse problems of this kind is to have massive quantities of data, which fortunately ion channels have. Foreshadowing the final solution, the inverse problem solution that Eisenberg produced is very well supported because his model can be used to design novel channels with the proper selectivity. The actual ionic concentration near charged surfaces in proteins is astronomically high. This is the clue to start with; such a crowded environment suggests that the finite size of the individual ions is crucial, and that the interactions between the tightly packed ions are crucial. Variational principles, Euler-Lagrange (that is, in contrast with PDEs) deal with this well. Eisenberg discussed several specific conclusions which are fleshed out in more depth in other talks at the meeting. The lively discussion following the talk centered on this last distinction.

Generalized Poisson Nernst-Planck equations for ion channel transport: Numerical schemes and modified models
Qiong Zheng (Michigan State University)

Dr. Zheng began by offering another perspective on the high relevance of ion channels in biology, emphasizing their role in taste and smell and in the cardiovascular system. Zheng follows this with a review of theoretical approaches to modeling these channels, concentrating on the Poisson-Nernst-Planck model (PNP) discussed elsewhere in the session. The complex geometry of protein structures, and the interface conditions of the protein, complicates the application of PNP to ion channels. Their numerical algorithms to deal with these issues are validated by comparison to experimental data obtained for the Gramacidin A ion channel. Finally, their differential-geometry approach was used to compute different current values as a function of the ion concentration, with good agreement to experimental data.

Modeling ion size effects with density functional theory of fluids
Dirk Gillespie (Rush University Medical Center, Chicago IL)

Dr. Gillespie presented density functional theory (DFT) as an approach to dealing with ion-ion correlations with good accuracy and controlled computational complexity. First, Gillespie reviews the limitations of thermodynamic approximations (such as Poisson-Boltzmann), which are not accurate, and full molecular dynamics simulations, which are very expensive computationally. DFT is an extension of a similar approach from quantum mechanics used to estimate steady-state concentrations as a method to account for ion-ion correlations. DFT showed reasonable agreement with Monte Carlo simulations of systems with two ions but is many orders of magnitude faster to compute; meanwhile, DFT is far more accurate than "mean field" approaches even when the finite ion sizes are taken into account. Generally speaking, the differences between DFT and other approximate methods are quite significant in many biologically relevant cases, for example, in the charge inversion layers along the surfaces of the pores in nanofluidic devices. For these devices, DFT gave a much better estimate of the current. Then, DFT was used to model conductance through a calcium-selective ion channel (the Ryanodine Receptor). Again, DFT was well-able to reconstruct the conductance of the channel at varying concentrations, and for various calcium salts, without additional free parameters. Finally, this approach offered physical and mechanistic insight because the DFT can be broken down into components corresponding to different physical properties of the ions.



Minami Yoda (Georgia Tech)

Title Unavailable
Chun Liu (Penn State University)

Dr. Liu prefaced his talk with a philosophical discussion on the merits of different languages to discuss mathematics and science, going back to the Opium wars and the early 20th century conflicts between China and Japan.

From this philosophical discussion, he segued to the link (via the underlying equations) between heat dissipation equations in fluids and the ideal gas law. This led to some of the energy functions used in other talks of this session. The balance of this talk is a broad review of the following topics: the different scales/components that can be integrated into a biophysical model, different approaches that can be used to optimize/solve such a model, and the different considerations that arise when such a model is treated deterministically or stochastically.

Fluid Assisted Charge Transport: Mathematical Consistency of the Navier-Stokes/ Poisson-Nernst-Planck Model
Joseph W. Jerome (Northwestern University)

The Navier-Stokes/Poisson-Nernst-Planck model is used to study the electrophysiology of the cell, although it has also been used in other applications, such as the development of microfluidic devices in biochip technology and in the study of electro-osmosis. Dr. Jerome discussed some approximations to the Navier-Stokes equation in great detail, and presented relevant lemmas and theorems. He concluded with a description of the dual-mixed hybridized/finite volume scheme, and a discussion of stability and error analysis of the method.

Quantum dynamics in continuum for proton channel transport
Duan Chen (Michigan State University)

Dr. Chen presented a continuum model to characterize a protein during transport through the pore of an integral membrane protein. Chen reviewed the particular relevance of protein translocation to the immune system and to core energy metabolism. Then he highlighted the core distinctions between proton conductance and the transport of other ions. Following the introductory material, he detailed the specifics of his multi-scale model. The solvent (water, ions, etc.) was modeled as a continuum, while the pore is modeled explicitly under the classical (in the sense of classical physics) energy function/framework developed by Guo-Wei (Wei et al) assuming a static structure for the channel protein. To these frameworks, Chen added a quantum mechanics model for the proton itself. Finally, this hybrid model was implemented in relatively low computational complexity (i.e. it runs fast), utilizing among other approaches previously characterized in the literature: Dirichlet to Neumann mapping, the matched interface and boundary method, Gummel iteration, and Krylov space techniques. The overall approach is validated by close agreement to experimental characterization of the Gramicidin A channel.

Molecular meshing and continuum modeling
Benzhuo Lu (Institute of Computational Mathematics and Scientific/Engineering Computing, Chinese Academy of Sciences)

The continuum modeling that Dr. Lu described can be used to overcome certain limitations of other biomolecular simulation methods, in particular problems related to time and length scales. He began by discussing continuum models used for electrostatics and diffusion, touching on the roles of Poisson-Nernst-Planck equations and the Poisson-Boltzmann equation in describing systems out of equilibrium. Lu also described how reaction rates may be predicted for diffusion-controlled enzyme-substrate reactions, and the effects of particle size. He concluded by introducing his group's recently-developed method for molecular surface meshing incorporated in the TMSmesh software tool, which can be used for macromolecular simulation using boundary element, finite element, or other numerical methods.

Towards a Self-consistent Electromechanical Model of Protein-Membrane Interactions
Yongcheng Zhou (Colorado State University)

These kinds of interactions are fundamental processes essential for proper signaling and membrane trafficking within cells. Mathematical models of reasonable fidelity and efficiency can contribute significantly to these important biological problems. The development of such models has long been a challenging task for biophysicists and applied mathematicians. Dr. Zhou used direct coupling of the Poisson-Boltzmann equation and nonlinear elastic equations in the development of his electromechanical PDE model. He detailed the application of this model to a study of how interactions with vesicles and Bin/amphiphysin/Rvs (BAR)-domain proteins contribute to membrane curvature.

THURSDAY, APRIL 28

Velocimetry and Thermometry in Microfluidic Devices
Minami Yoda (Georgia Institute of Technology)

Dr. Yoda's talk reviewed current velocimetry and thermometry capabilities in internal flows of aqueous solutions. These methods give time-averaged velocity and temperature fields at spatial resolutions of a few micrometers or less; however, the most common techniques are still unable to resolve flows at scales relevant to proteomics and genomics, biochemical sensing, and drug delivery, and nearly all such methods are still being developed in university research laboratories. Methods discussed in Yoda's talk include microscale particle-image velocimetry, multilayer nano-particle tracking velocimetry, dual-tracer fluorescence thermoetry, and evanescent wave-based fluorescence thermometry.

Understanding lung surfactant via coarse-grained molecular dynamics simulations
Ronald G. Larson (University of Michigan, Ann Arbor)

Lung surfactant is a mixture of lipids and proteins that lines the air/water interface of the alveoli and decreases the work involved in breathing. Dr. Larson utilized the MARTINI coarse-grained force field to simulate lipid monolayers during the compression and re-expansion, to determine the effect of monolayer components on lung surfactant functioning. Particular emphasis was placed on the phase and collapse transitions of monolayers containing the primary lipid component of lung surfactant dipalmitoylphosphatidylcholine (DPPC) with additional components including unsaturated lipids, palmitic acid, cholesterol, and hydrophobic surfactant proteins. Larson's simulations elucidated some of the mechanisms involved in physiological surface tension reduction, providing information on a length and time scales that are not experimentally accessible.

Multiscale simulation of liquids under confinement
Narayan Aluru (University of Illinois at Urbana-Champaign)

Since the physics of fluids at the nanometer scale can be quite different from the macroscopic physics, there is considerable interest in developing techniques to elucidate nanoscale fluid phenomena. Despite recent advances, many fundamental questions concerning fluid physics still remain, including those related to fluid confinement and the role of surface charge, chemical functionalization and wall structure. Dr. Aluru described how computational approaches can provide fundamental and unique insights into fluid physics at the nanoscale. He discussed some of the limitations of classical theory embodied in the Poisson-Boltzmann and Navier-Stokes equations. He then showed that multiscale methods combining density functional theory, atomistic molecular dynamics, mesoscale particle transport and quasi-continuum theories can be used to address some of the fundamental questions posed above, and described results of the application of these methods to the study of fluid transport through carbon nanotubes, boron nitride nanotubes, and solid-state nanopores.

Structure and dynamics of the water/amorphous silica interface
Sherwin J. Singer (The Ohio State University)

Dr. Singer introduced the problem of electrokinetic transport in nanochannels; transport that appears to be governed by a surface charge that is less than the actual one. He described some models of charged surfaces, including the Gouy-Chapman-Stern model. Results of simulations performed by Dr. Singer show (i) no ion mobility where water is immobile, and (ii) surface conductivity that is comparable to experimental values. Biomolecular applications were also described.

FRIDAY, APRIL 29

Can we personalize therapy for kidney disease using mathematics?
Brad Rovin (The Ohio State University College of Medicine)

Dr. Rovin introduced the topic of personalized medicine by noting how diseases that affect the kidney show remarkable inter-individual heterogeneity, making it difficult for a single type of therapy to be successful for all individuals. He used biomarker discovery to identify proteins that predict the course of an individual's disease. In order to understand the dynamics of the kidney disease associated with systemic lupus erythematosus, Rovin has started developing (in collaboration with investigators at the MBI) models that capture the multiple time-dependent interactions among the biomarkers and other disease variables. The model provides results that are in good qualitative agreement with clinical behavior, and has proven to be useful in evaluating therapeutic strategies for individual patients.

In vitro models of glomerular permeability
Nicholas Ferrell (Cleveland Clinic)

Dr. Ferrell gave a basic description of the function of the kidney function, which retains protein and other high molecular weight solutes in the blood while freely filtering water and low molecular weight solutes. This function is dependent on a number of nanoscale phenomena including nanofluidic flow of water, electrolytes, and protein across the glomerular capillary wall and charge interactions within the glomerular filter. Ferrell developed a silicon nanopore hemofiltration membrane to perform filtration in a miniaturized bioartificial kidney, a nanofluidic platform that, along with other in vitro protein gel models of the glomerular basement membrane (GBM), has provided insight into the underlying principles of glomerular selectivity and filtration across biological membranes in general.

Summer Education Programs

PROGRAM IN MATHEMATICAL BIOLOGY FOR UNDERGRADUATES

June 20-July 1, 2011

The summer of 2011 marked the MBI's sixth annual Summer Program for Undergraduates that includes a two-week active survey of mathematical biology followed by a six-week Research Experience for Undergraduates (REU).

The first week of the program involved tutorials and hands-on computer labs in mathematical bioscience topics. The first day saw Dennis Pearl presenting key issues in statistical phylogenetics – aligning molecular sequences and inferring evolutionary trees. In the afternoon, David Gerard led a computer lab, giving students a chance to try out the ClustalX alignment program along with PAUP and MrBayes phylogenetics software. On Tuesday, Victor Jun lead a morning tutorial covering selected topics in bioinformatics such as using databases, and analyzing and visualizing microarray and ChIP data. That afternoon, Xun Lan guided the students in trying out online bioinformatics software. Janet Best presented a lively mathematical neuroscience tutorial focusing on neural rhythms the following day and Jung Eun Kim led the afternoon computer lab using XPPAUT and Matlab. Thursday saw Joe Verducci presenting issues in the quantitative analysis of chemogenomic data leading to an introduction to the SCOOP method (Shrunken Centroid Ordering by Orthogonal Projections) for selecting differentially expressed genes, while Katie Thompson supervised the afternoon computer lab using the R package and the BioCoductor and SCOOP R programs. The week concluded with Tao Shi's tutorial on using exploratory data analysis tools in environmental statistics and Jinguo Gao's afternoon computer lab using R.

Dividing into teams, the students were given a chance to study a real problem in their chosen topic area during the second week of the program. The two-week survey concluded with each of five teams participating in a mini-conference, making both poster and oral presentations on their projects. The mathematical neuroscience team (Kiah Hardcastle, Junfei Huang, and Jesus O'Neill) presented their studies of the sleep cycle using oscillatory processes with many time scales. The phylogenetics project team (Yan Lu and Xuan Zhu) presented an analysis of the evolution of Penguins combining both molecular data and morphological characteristics of the birds. Next, the environmental statistics group (Jamie Prezioso and Hanna Chakoian) described their study of climate change using 130 years of temperature data, combined with CO2, CH4, and Solar Radiation data over the last 50 years. The bioinformatics project, presented by Alice Shen and Dinesh Manandhar, explored regulatory protein networks in leukemia cells using motif mining and protein network visualization techniques. Finally, the chemogenomics team of Nitish Aggarwal, Hong Tran, and Brian Kinney, compared the use of the SCOOP method to other techniques in the literature for discovering genes associated with the early detection of breast cancer. The collaborative nature of all of these efforts was illustrated as each student presented a substantial part of their team's work.

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 Pearlly Yan guided the students through the computationally intensive work of the lab. Joe Travers opened his neuroscience lab to a tour of their work in the signaling processes associated with taste and, 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.

At the conclusion of the two-week program, the REU component of the summer program then provided six students the opportunity to spend the remaining part of the summer going into much more depth in a research project in their chosen area. Junfei Huang's project involved an analysis of a two-process model for insomnia and what it would predict about the behavior of Serotonin levels and the EEG response. Jesus

O'Neill worked on a related project to investigate the role of Serotonin in the link between depression and insomnia. Hong Tran examined SCCOP, cross-validation, and some novel Support Vector Machine methodologies for the early detection of breast cancers using only expression data from a non-invasive peripheral blood assay. Yan Lu and Xuan Zhu worked as a team in using Bayesian phylogenetic methods to investigate the relationship of clinical behavior and transmission dynamics to the evolution of several hundred strains of HIV. Finally, Dinesh Manandhar's REU project involved bioinformatic studies of histone modifications in three cell lines of varying degrees of differentiation to find some previously undiscovered epigenetic differences.

All of the students taking part in the MBI undergraduate summer program were exposed to new areas of scholarship and gained an increased appreciation for the mathematical biosciences. Presentations from the tutorials and mini-conferences are viewable on the MBI website at http://mbi.osu.edu/eduprograms/undergrad2011.html.

MBI-NIMBIOS-CAMBAM GRADUATE WORKSHOP ON MATHEMATICAL ECOLOGY AND EVOLUTION

July 25-August 5, 2011

Members of the organizing committee were: Fred Guichard (McGill); Suzanne Lenhart (UT Knoxville); Yuan Lou (OSU); and Libby Marschall (OSU). A total number of 41 graduate students from departments of mathematical and biological sciences participated in this workshop.

Topics included *infectious disease, resource management, invasive species* and *evolution biology*. The program featured ten researchers from the mathematical and biological sciences, each of them worked with the students for one day. The speakers gave lectures in the mornings, followed by afternoon computer and analysis activity including work on projects, assisted by nine MBI and CAMBAM Postdoctoral Fellows. Initial feedback from participants indicated that they very much appreciated this great opportunity and that they were challenged by the breadth and depth of the lectures and lab sessions. The following is the full list of speakers and their lectures:

- Linda Allen (Texas Tech) *An Introduction to Stochastic Epidemic Models*
- Ed Allen (Texas Tech) *A Practical Introduction To SDEs and SPDEs in Mathematical Biology*
- Chris Cosner (U Miami) *Modeling the Evolution of Conditional Dispersal in Spatially Heterogeneous Environments*
- Fred Guichard (McGill) *Spatial pattern formation in ecological systems*
- Ian Hamilton (OSU) *Modeling the evolution of social behavior using evolutionary game theory*
- Alan Hastings (UC Davis) *Bifurcations, time scales, and regime shifts*
- Suzanne Lenhart (UT Knoxville) *Introduction to Optimal Control with Applications to Population and Disease Models*
- Lea Popovic (Concordia) *Macroevolution and Phylogenetic Tree Models*
- Robin Snyder (CWRU) *Modeling the effects of environmental variation in space and time using transfer functions*
- Joe Tien (OSU) *An introduction to mathematical epidemiology and cholera in Haiti*

In addition to these lectures, Avner Friedman (Ohio State University) gave a talk at the workshop on *Cancer as a multifaceted disease* on Thursday August 4, 11am – noon.

During the workshop each student worked on one research project in a team of 4-6 participants. There are a total number of eight team projects in this workshop. A Mini-Symposium was held on the final day of the workshop. Each group presented their results to the entire group of participants and other audiences. The Mini-Symposium atmosphere was lively and scientifically stimulating. The titles and slides of these presentations are available on the MBI web site http://www.mbi.osu.edu/eduprograms/graduate2011schedule.html

Seminars 2010-2011

COLLOQUIUM

KC Huang, Biochemistry and Electrical Engineering, Stanford University
Physical mechanisms for bacterial cell shape determination (October 11, 2010)

HT Banks, Center for Research in Scientific Computation, Center for Quantitative Sciences in Biomedicine, N.C. State University
Relaxed Controls, Preisach Hysteresis, And Mixing Distributions In Statistical Inverse Problems (October 18, 2010)

Daniel Schoenberg, Center for RNA Biology and Department of Molecular and Cellular Biochemistry, The Ohio State University
Re-capping messenger RNAs in the cytoplasm: A new aspect of gene expression that redefines the scope of the transcriptome (November 8, 2010)

Stephen Ellner, Ecology and Evolutionary Biology, Cornell University
Rapid evolution: coupling ecological and evolutionary dynamics (November 15, 2010)

Thierry Emonet, Molecular, Cellular and Developmental Biology, Yale University
Chemotaxis of the individual bacterium (November 22, 2010)

David Cowburn, Albert Einstein School of Medicine
Nmr/structural biology - future promise needs new applied math (January 24, 2011)

Daniel Janies, OSU Medical Center
Assembling the tree of life (January 31, 2011)

Mike Reed, Mathematics, Duke University
Mathematical models of serotonin metabolism: What is the mechanism of action of SSRIs? (February 7, 2011)

Katia Koelle, Duke University
A dimensionless number for understanding the evolutionary dynamics of antigenically variable RNA viruses (February 28, 2011)

Hugh R. Wilson, Director, Centre for Vision Research Fellow, Canadian Institute for Advanced Research Professor of Biological & Computational Vision
Nonlinear Dynamics of Binocular Rivalry & Migraine Auras (March 7, 2011)

A.J. Hudspeth, Laboratory of Sensory Neuroscience, The Rockefeller University
Making an effort to listen: mechanical amplification by myosin molecules and ion channels in hair cells of the inner ear (March 28, 2011)

David Botstein, Molecular Biology, Princeton University
Extracting Biological Insight from Complex Genome-Scale Data: Connecting Growth Control and Stress Response in Yeast (April 11, 2011)

Qing Nie, Director, Center for Mathematical and Computational Biology, Mathematics, and Biomedical Engineering, UC Irvine
Noise Attenuation in Biological Systems (April 18, 2011)

Qiang Du, Penn State University
Diffuse interface modeling of biomimetic membranes (May 9, 2011)

George Karniadakis, Applied Mathematics, Brown University
Multiscale Modeling of Hematological Disorders (May 23, 2011)

POSTDOC SEMINARS

Dan Siegal-Gaskins, MBI, Ohio State University
Network motifs and complex tissues (September 16, 2010)

Yunjiao Wang, MBI, Ohio State University
Patterns of Rigid Solutions of Coupled Cell Systems (September 23, 2010)

Harsh Jain, MBI, Ohio State University
Impact of treatment on mutation acquisition in prostate cancer (October 14, 2010)

Kun Zhao, MBI, Ohio State University
Blowup for some reaction-cross diffusion models in population dynamics (October 21, 2010)

Julia Chifman, MBI, Ohio State University
A systems biology approach to iron metabolism in cancer cells (November 4, 2010)

Carl Toews, MBI, Ohio State University
An Inverse Problem Arising in Cardiology (November 18, 2010)

Chuan Xue, MBI, Ohio State University
A mechanochemical model of chronic wound healing (December 2, 2010)

Rebecca Tien, MBI, Ohio State University
The Decline of Calanus finmarchicus in the Gulf of Maine: Using Modeling to Investigate the Relative Role of Top-down Verses Bottom-up Processes (December 9, 2010)

Deena Schmidt, MBI, Ohio State University
Linking network structure and stochastic dynamics to neural activity patterns involved in sleep-wake regulation (December 16, 2010)

Juan Gutierrez, MBI, Ohio State University
Genetic Control of Invasive Species (January 6, 2011)

Rachel Leander, MBI, Ohio State University
Using Optimal Control Theory to Identify Topological Structures that Promote Synchrony (January 13, 2011)

Richard Gejji, MBI, Ohio State University
Macroscopic model of self-propelled reversing bacteria (January 20, 2011)

Casey Diekman, MBI, Ohio State University
Modeling the Electrical Activity of the Mammalian Circadian Clock (January 27, 2011)

Matt Miller, Mathematics, University of South Carolina
Fiddler crab aggregation under predation: Questions about animal groups (February 10, 2011)

Gabriela Gomes, Theoretical Epidemiology, Instituto Gulbenkian de Ciencia
Measures of immunity across scales (February 17, 2011)

Tyler McMillen, Mathematics, Cal St. Fullerton
Learning to decide (nearly) optimally (March 3, 2011)

Jason Hsu, Statistics, Ohio State University
Multiple Testing in Biomarker Studies for Personalized Medicine (March 8, 2011)

Marisa Eisenberg, MBI, Ohio State University
Exploring cholera transmission dynamics using identifiability and parameter estimation (March 10, 2011)

Annie Lindgren, MBI, Ohio State University
Using next-generation sequence data to uncover the molecular basis for convergent evolution in the cephalopod cornea (March 31, 2011)

Rasmus Hovmoller, MBI, Ohio State University
Effects of missing data on species tree estimation from gene trees under the coalescent (April 14, 2011)

Paul Hurtado, Applied Mathematics, Cornell University
Infectious disease ecology: Immune-pathogen dynamics, and how trophic interactions drive prey-predator-disease dynamics (April 21, 2011)

Shu Dai, MBI, Ohio State University
Use noise to determine cardiac restitution with memory (May 5, 2011)

Suzanne Robertson, MBI, Ohio State University
Modeling waterborne disease: Incorporating heterogeneity in multiple transmission pathways (May 12, 2011)

Sam Handelman, MBI, Ohio State University
Phylogenetic Path to Event (PhyloPTE) (May 19, 2011)

Abdul-Aziz Yakubu, Chair, Mathematics Department, Howard University
Constant and Periodic Proportion Harvest Policies: Dynamic Implications in the Pacific Halibut and Atlantic Cod Fisheries (June 2, 2011)

Shari Wiley, Mathematics, Howard University
Harvesting and predator-prey interaction in a Georges Bank food chain (June 9, 2011)

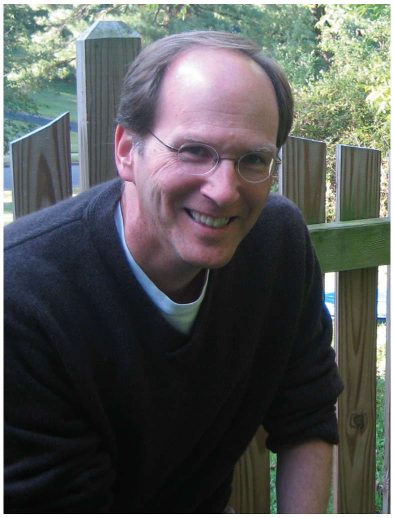
SPECIAL SEMINARS

Michael Reed, Mathematics, Duke University
The Auditory System for Mathematicians (August 13 , 2010)

Ian Stewart, Department of Mathematics, University of Warwick, UK
The Mathematics of Life (September 13, 2010)

John Cain, Virginia Commonwealth University
Kinematic Models of Paced Cardiac Fibers (October 22, 2010)

Public Lectures



STEVEN STROGATZ

**Theoretical and Applied Mathematics,
Cornell University**

THE MATHEMATICS OF GETTING IN SYNC

OCTOBER 12, 2010

Every night along the tidal rivers of Malaysia, thousands of male fireflies congregate in the mangrove trees and flash on and off in silent, hypnotic unison. This display extends for miles along the river and occurs spontaneously; it does not require any leader or cue from the environment. Similar feats of synchronization occur throughout the natural world, whenever large groups of oscillators interact. This lecture will provide an introduction to the math and science of synchronization. Amazing videos of synchronous fireflies and London's wobbly Millennium Bridge will be shown.

JIM KEENER

**Distinguished Professor of Mathematics,
Adjunct Professor of Bioengineering, University of Utah**

HEART ATTACKS CAN GIVE YOU MATHEMATICS

FEBRUARY 15, 2011

What is similar about football fans, a forest fire and a heart attack? The answer: Certain features of their behavior have a common mathematical description. As a result we can learn something about heart attacks from the behavior of crazed football fans.

A heart attack occurs when there is an occlusion of a coronary artery leading to tissue damage (and is rarely the result of math anxiety!). A heart attack is fatal when there is a subsequent disruption of the normal electrical signal of the heart, leading to fibrillation.

The purpose of this talk is to show how mathematics can help us understand more about fatal cardiac arrhythmias, how they occur, what they are, and how they might be eliminated or prevented.

RICHARD TAPIA

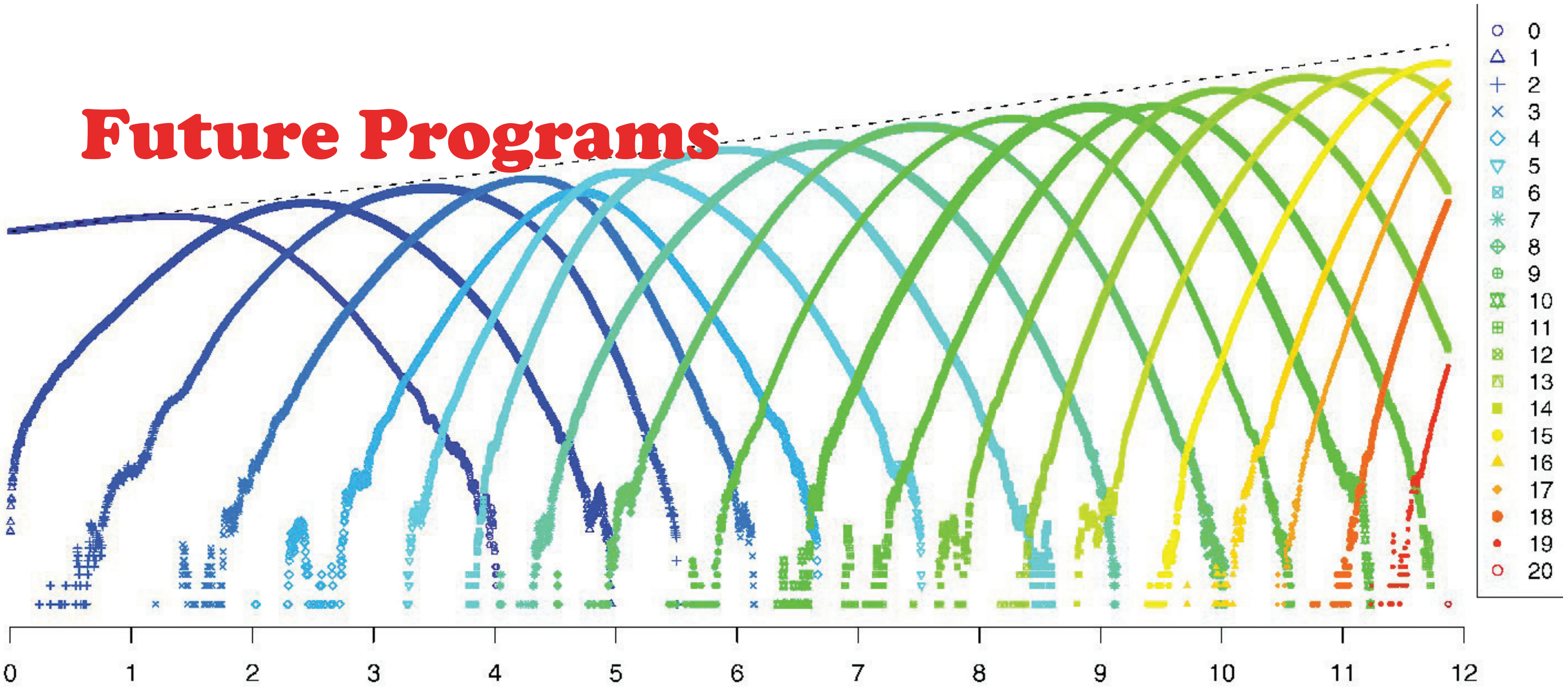
University Professor Maxfield-Oshman Professor in Engineering, Department of Computational and Applied Mathematics (CAAM), Rice University

MATH AT TOP SPEED: EXPLORING AND BREAKING MYTHS IN THE DRAG RACING FOLKLORE

NOVEMBER 4, 2010

Throughout his life, either as participant, support individual, or involved spectator, the speaker has been involved in some aspect of drag racing. As such he has witnessed the birth and growth of many myths concerning dragster speed and acceleration. In this talk the speaker uses his mathematical training to identify elementary mathematical frameworks for the study of a particular popular belief and then applies mathematics to better understand the belief at hand. In this manner some myths are explained and validated, while others are destroyed. Included in these examples will be attempts to determine how fast dragsters are really going, what is the maximum acceleration achieved , and what is the acceleration curve profile of today's dragsters? The speaker will explain why dragster acceleration is greater than the acceleration due to gravity, an age-old inconsistency and present his "Fundamental Theorem of Drag Racing." The first part of the talk will be a historical account of the development of the sport of drag racing and will include shots of various family members. A component of the presentation will be several lively videos used to illustrate points.

Future Programs



STOCHASTICS IN BIOLOGICAL SYSTEMS

July 2011 - June 2012

ORGANIZING COMMITTEE

- Linda Allen (Mathematics & Statistics, Texas Tech University)
- Richard Durrett (Mathematics, Duke University)
- Timothy Elston (Physics, Georgia Institute Technology)
- Thomas Kurtz (Mathematics, University of Wisconsin-Madison)
- Reinhard Laubenbacher (Virginia Bioinformatics Institute, Virginia Tech)

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.

WORKSHOPS

- *Workshop for Young Researchers in Mathematical Biology* (August 29 - September 1, 2011)
- *Workshop 1: New Questions in Probability Theory Arising from Biology* (September 12-16, 2011)
- *CTW: Spatio-Temporal Dynamics in Disease Ecology And Epidemiology* (October 10-14, 2011)
- *Workshop 2: Stochastic Processes in Cell and Population Biology* (October 24-28, 2011)
- *CTW: Free Boundary Problems in Biology* (November 14-18, 2011)
- *Workshop 3: Robustness in Biological Systems* (February 6-10, 2012)
- *CTW: Recent Advances in Statistical Inference for Mathematical Biology* (February 20-24, 2012)
- *Workshop 4: Evolution and Spread of Disease* (March 19-23, 2012)
- *Workshop 5: Spatial Models of Micro and Macro Systems* (April 16-20, 2012)
- *CTW: Tissue Engineering and Regenerative Medicine* (April 30 - May 4, 2012)
- *Workshop 6: Algebraic Methods in Evolutionary and Systems Biology* (May 7-11, 2012)
- *CTW: Statistics, Geometry, and Combinatorics on Stratified Spaces Arising from Biological Problems* (May 21-25, 2012)

MATHEMATICAL NEUROSCIENCE

July 2012 - June 2013

ORGANIZING COMMITTEE

- Carmen Canavier (Neuroscience, Louisiana State University)
- John Rinzel (Center for Neural Science, New York University)
- Steven J. Schiff (Penn State Center for Neural Engineering)
- Eric Shea-Brown (Applied Mathematics, University of Washington)
- Murray Sherman (Neurobiology, University of Chicago)

In 2012-13 MBI will return to mathematical neuroscience, which was the subject of its first emphasis year in 2002-3. Mathematics both elucidates key dynamical mechanisms for patterns of neural activity and quantifies levels of information in these patterns. At the same time, new mathematical questions and techniques, that often bridge information theory, dynamical systems, and statistical mechanics, have been inspired by the complexity of the underlying networks and the computations they perform. Over the past decade, mathematics has entered new subfields of neuroscience, and has begun to suggest unexpected parallels among others. (W1) We will open the emphasis year with a workshop focusing on such parallels, in the form of general challenges posed by dynamics of nonlinear, spiking networks, and will organize a series of workshops to follow that will highlight mathematical impact and possibilities in the most active and exciting areas of neuroscience.

Cognitive neuroscience (W2) presents superb opportunities for mathematical contributions, especially in connecting different theoretical and experimental frameworks. On the experimental side, methods ranging from single-neuron recording to human behavioral tests are flourishing, and mathematical models are beginning to suggest how one leads to the other. Rigorous theoretical treatments from microeconomics are often applied, including Bayesian estimation and optimization, but details of how they might be implemented in stochastic, dynamic neural circuits have only recently been proposed. By bringing together theorists working on different levels, a workshop will move the field closer to a long-held goal of understanding and predicting decision-making and choice behavior.

Another timely and exciting workshop will be the dynamics of neural disease (W3). Recent work has suggested mechanisms for pathological activity patterns in epilepsy and Parkinsons disease, and dynamical models have been used to explain the function and possible improvement of stimulation-based therapies. Mathematical analysis is also being pursued for prosthetics used in sensory systems (i.e., cochlear implants for deafness) and motor systems (i.e., neural implants that drive artificial limbs). Many open questions remain for other disease states, including addictions, mental illnesses, and memory dysfunction. In parallel, rich mathematical questions arise in the exploding area of non-invasive imaging. Algorithms are needed for more efficient data analysis and especially for combining datasets gathered on different spatial and temporal scales (e.g., fMRI, EEG, and single-neuron recordings).

A fourth workshop (W4) will focus on rhythms and oscillations. This field was featured in the 2002-03 emphasis year, and continues to be highly exciting - especially due to increasing evidence that oscillations and appropriate phase relationships are critical for cognitive states and sensory processing.

Moving to the smallest spatial scale, the chemical and molecular mechanisms for the dynamics of brain state regulation, development, repair, and adaptation are being uncovered by modern tools of molecular biology and genetics. These small-scale dynamics affect excitability, and bridging across such multiple scales is a frontier in our understanding of patterns of neuronal activity. There is enormous opportunity for mathematics to contribute by combining models at the levels of systems biology and electrophysiology. We will focus a workshop (W5) on this theme.

In a workshop on sensory systems (W6), we will address separate modalities, as well as consider commonalities for the representation and processing of stimuli with naturalistic statistics. Here, the establishment of maps and associations, the dynamics of synaptic plasticity, the adaptation to scene statistics, and the mechanisms for multi-modal interactions are of central importance. Special focus will be given to active sensing and feedback loops (central to periphery) in sensory processing, to coding strategies, and to streaming (source separation) in the auditory system. Attention throughout the workshop will be given to plausible neuronal mechanisms for these aspects of sensory processing.

WORKSHOPS

- *MBI BioSciences Problem-Solving Workshop* (PSW@MBI) (July 16-20, 2012)
- *Workshop 1: Mathematical Challenges in Neural Network Dynamics* (October 1-5, 2012)
- *CTW: Mathematical and Computational Challenges in Cilia- and Flagella-Induced Fluid Dynamics* (October 15-19, 2012)
- *CTW: Statistics of Time Warpings and Phase Variations* (November 13-16, 2012)
- *Workshop 2: Cognitive Neuroscience* (December 10-14, 2012)
- *Workshop 3: Disease* (February 4-8, 2013)
- *Workshop 4: Rhythms and Oscillations* (March 18-22, 2013)
- *Workshop 5: Cellular and Subcellular* (April 8-12, 2013)
- *Workshop 6: Sensory Systems and Coding* (May 6-10, 2013)

Publications

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Cladistics Vol. 26 No. 1 (2010) pp. 1-13

Y. KIM AND A. FRIEDMAN
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Y. KIM AND A. FRIEDMAN
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Y. KIM, J. WALLACE, F. LI, M. OSTROWSKI AND A. FRIEDMAN
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Journal of Mathematical Biology Vol. 61 No. 3 (2010) pp. 401-421

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2009 Proceedings of the Fourth SIAM Conference on Mathematics for Industry (2010) pp. 84-92

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Using nonlinear model predictive control to find optimal therapeutic strategies to modulate inflammation
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A. FRIEDMAN, B. HU AND C. XUE
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Transformed Epithelial cells (TEC) and fibroblasts/myofibroblasts interaction in Breast Tumor: A Mathematical Model and Experiments
Journal of Mathematical Biology Vol. 61 No. 3 (2010)

A. M. OSTER, B. THOMAS, D. TERMAN AND C.P. FALL
The mitochondrial permeability transition pore confers excitability and CICR wave propagation
J Theor Biol Vol. 273 No. 1 (2011) pp. 216-31

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